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Describing cognitive and mood assessments in acute stroke

A thesis by

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Submitted for the degree of Doctor of Philosophy

To

The University of Glasgow

From

The Institute of Cardiovascular and Medical Sciences

College of Medical, Veterinary and Life Sciences

University of Glasgow

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Abstract

Background

Stroke is the foremost medical condition responsible for acquired disability and dependency. The initial psychological and physical deficits should arguably be identified early to allow interventions to be put in place if potential long-term sequelae are to be minimised.

Physical impairments within stroke cohorts have been extensively researched and reported. We have access to numerous scales that describe general physical functioning during daily activities and its effects on independence and quality of life. Deficits in movement are easily identified and attributes of physical movements can be associated with such obvious measurement terms as strength, speed, co-ordination and task completion. As these attributes can be graded, it is simple to compare patients over time, within stroke cohorts and against the general population: controlled studies are straightforward, even if natural biological variation demands large samples.

However, though physical impacts on a patient may be easily observed and measured, corresponding deficits in cognition and mood are less easily detected and quantified. Psychological problems are common within stroke populations, and exert both short and long term effects throughout all stages of rehabilitation. Despite our awareness of the potentially critical effects of psychological factors on patient outcome, there is a dearth of high quality research in this area. Although many cognitive and mood assessments are available, including some that were developed specifically for use in stroke, these are neither regularly administered nor have been convincingly shown to be accurate and reliable in identifying specific deficits. Thus, it is understandable that research available to us that describes prevalence and effects of cognitive and mood problems post-stroke is sparse in comparison to our knowledge of physical deficits.

Methodology

In order to begin to understand the effects that cognition and mood have on patient outcome post-stroke, a way of identifying prominent issues is required. Knowing that their effects can have both short and long term impact, reliable screening beginning early after stroke onset could offer opportunities to improve patient outcome through early implementation of interventions.

Before an appropriate screening tool can be selected, evidence is required to support its feasibility and accuracy within acute stroke cohorts. In this thesis, I investigate cognitive and mood-screening assessments in stroke, across a series of linked projects.

I carried out a review of the current research and I surveyed stroke units to identify which cognitive and mood assessments are commonly implemented. I collated and offer synthesis of the published data on accuracy of cognitive assessment instruments. I used these results to inform a diagnostic test accuracy study, examining selected measures that are commonly used in UK practice to screen for cognitive and mood problems. Based on these results, I designed (and was awarded grant funding for) a clinical study to assess test properties of cognitive and mood screening instruments in a rehabilitation setting and to describe potential obstacles affecting patient assessment.

Findings

There is heterogeneity in the choice of cognitive and mood tests employed across research and clinical practice. There was some overlap in assessment choice within these domains but no clear consensus on a preferred assessment tool. This is in part explained by the substantial number of tests available, it is telling that the most popular assessments accounted for only a fraction of the tool assessments employed. My literature based work also points to a relative lack of published science employing a cognitive or mood assessment tool.

My review of diagnostic test accuracy found that properties of cognitive tools commonly used in practice and research (Folstein's Mini Mental State Examination: MMSE, the Montreal Cognitive Assessment: MoCA, the Addenbrookes' Cognitive Examination Revised: ACE-R and the Cambridge Cognitive Examination revised: R-CAMCOG) were susceptible to changing populations and purpose of assessment, with test properties differing when screening tools are used in acute and chronic stage of stroke. Depending on the cut-offs that are used to define "screen positive" cases, these tools would have varying ability to identify multi-domain cognitive impairment or dementia. Generally when applying standard (i.e. the traditional cut-off described for test use in an unselected population) cut-offs, sensitivity was good but specificity was low. Specificity could be improved when the cut-offs were altered while maintaining reasonable sensitivity and this suggests that screen positive thresholds may need to be altered to suit a stroke population. The need for lowering our standard cut-offs suggests that there may be factors present in typical acute stroke patients which affect assessment accuracy compared to the populations and purpose for which these scales have been developed.

Using the MOCA in the acute setting of my clinical study, confirmed that stroke cohorts require altered cut-offs to improve accuracy in cognitive impairment detection. A stroke cognitive assessment that can be derived from a standard neurological examination (the Cog4) has been described. Cross sectional comparison of MoCA and Cog 4 suggest that Cog4 has questionable validity and stroke specific cognitive measures are required since scores derived from other types of measures are not necessarily testing the most appropriate domains for stroke deficits.

A lack of published data on cognitive and mood screening in the first days post-stroke suggested that describing the feasibility of assessing stroke patients in an acute setting would be a useful topic for research. My subsequent clinical study incorporated verbal and non-verbal assessments for mood and the MOCA. As well as usual test accuracy outcomes I considered feasibility issues such as proportion of patients suitable for initial approach, acceptance of assessment, prevalence of common stroke related impairments that mandate assistance or cause difficulty in

completing assessments, or that preclude assessment altogether. A moderate proportion of patients who were approached declined to take part and several others required external assistance to complete the assessments. Shorter, less cognitively demanding assessments required less assistance and appeared to offer higher accuracy for predicting mood problems at follow-up. These results suggest that delaying cognitive and mood assessments until later during the post-stroke period may reduce the interference from acute stroke deficits.

The final piece of work generated from my PhD studies, and that is ongoing, continues the theme of feasibility of cognitive and mood assessments. Cognitive and mood assessments are performed in stroke rehabilitation centres. The rehabilitation setting was chosen, as it will include varying patterns of physical and cognitive impairment. By comparing brief assessments and more lengthy measures of cognition, I hope to identify the most appropriate testing scheme that minimises patient burden. As part of this work I will describe the impact of stroke deficits on assessment and quantification of the patient's psychological capabilities.

Conclusions

In conclusion, these studies have demonstrated a lack of guidance and of protocols for cognitive and mood assessment post-stroke. The evident heterogeneity in choices of assessment in research and usual practice indicated a need for evidence based accuracy studies. In conducting these I found that usual measures are susceptible to the population, timing, and cut-off used to define test positive cases, together indicating undesirable sources of variation. Transient stroke-related problems may lead to overestimation of persistent impairments. Although acute screening of cognition and mood would be possible, such screening may not be widely acceptable to patients and would require a high level of assistance from health professionals. Acute screening should only be performed if there are potential benefits that could impact on the patient from identification of cognitive or mood problems at this early stage. With the transient changes in cognition and mood that the majority of stroke survivors experience, screening is best left until later in the patient journey. However, there may still be potential feasibility issues

of administration and assessment completion during later stages. Therefore, I suggest that studies that investigate what assessments are feasibly administered to stroke patients in later stages are required. This will inform future trial recruitment for complete data requirements as well as provide clearer picture of stroke survivors' affected cognitive domains and or mood problems.

Figure 1 Flow chart of research strategy, chapter influence and ethical approval

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Chapter 1 Introduction

1.1. Epidemiology of stroke and stroke related disability

Stroke is the second highest cause of death in the developed world (10% of deaths)(1), and the main cause of adult disabilities in Europe and the USA(2). Each year, 15 million people worldwide have a stroke. Of these 5 million die and 5 million suffer lasting impairment.(1) Frequency of ischaemic stroke ranges between 85-90% of all strokes versus 10-15% for haemorrhagic stroke (hospitalised and community settings).(3-5)

In a community sample, 88% of stroke survivors had some form of motor deficit.(6) It is estimated that six million Europeans are living with a stroke related impairment(7). The greatest rate of functional recovery takes place by 3 to 6 months post-stroke.(6, 8) At least half of survivors experience significant functional disability a year after their stroke(9). More motor deficits are present in stroke survivors greater than 75 years old, but recovery is associated with stroke severity and not age (6).

Common impairments are weakness in limbs (especially in the upper limb 77.4%)(10) with long term arm movement difficulties affecting 40%, sensation changes about 80%, and visual disturbances around 66% (11). Other physical problems include: incontinence (48.2%)(10)- 15% continuing to suffer with incontinence at 1 year post-stroke.(11)

Haemorrhagic stroke patients have a higher incidence of severe headaches, convulsions(4) as well as an (up to four times) increase in mortality in the first 3 months post-stroke(5), but lower incidence of paresis and sensory deficits than ischaemic stroke survivors.(4)

Physical impairments are well described within the epidemiology of stroke but this is not true for cognitive and mood impairments.

1.1.1. Post-stroke cognitive impairments

Cognitive and mood impairments are common after stroke affecting around one third of survivors.(11-13) Cognitive domains commonly affected are: attention, orientation, language and memory (14, 15) with a general cognitive impairment profile of more pronounced deficits in executive function and attention processing assessment.(16)

Stroke is a major risk factor for developing dementia, the risk increasing with age from 15% at 60-69 years to 36% in those over 80 years; and it increases over time with an incidence of 9-17% at 1 year to 33% by 5 years. However, 7-16% of survivors had pre-stroke dementia that only becomes apparent post-stroke. (13, 17)

1.1.2. Mood impairments post-stroke

Prevalent mood problems are depression and anxiety.(18) Mood disorders post-stroke, especially depression, are associated with previous strokes, social activity decline and living alone. There are four main stroke related features that render survivors susceptible to developing depression. These are: physical impairments and fatigue which reduce involvement in activities; other medical problems which can add to the stress independent of the stroke; experience of a stroke can lead to a more negative way of thinking; cognitive impairments affecting the way in which information is processed.(19) Post-stroke cognitive problems, however, are a main risk factor, accounting for 42% of mood changes.(20, 21)

1.2. Nosology of post-stroke cognitive problems

Cognitive impairments post-stroke are integrated in nature and have overlapping features; this poses difficulty for clinical assessment and to distinguish criteria for classification.(22, 23) This had led to broad terminology being used to cover all

types of dysfunction. In an attempt to clarify the various cognitive problems that can be seen post-stroke, I have provided definitions of the most common problems. Figure 1-1 attempts to illustrate the various cognitive impairments found post stroke and how they overlap.

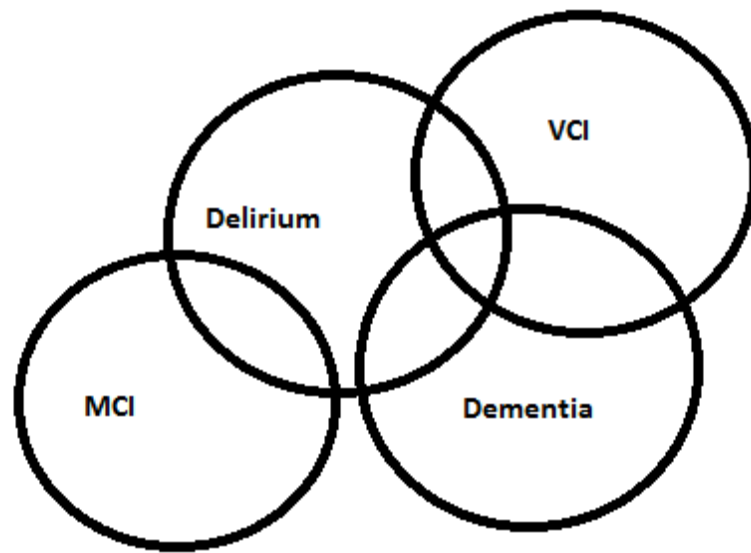


Figure 1-1 Venn diagram of post-stroke cognitive complications

MCI= Mild Cognitive Impairment, VCI=Vascular Cognitive Impairment

1.2.1. Delirium

Delirium is a cause of cognitive impairment. It is defined as a “multifactorial neuropsychiatric syndrome with numerous predisposing and precipitating factors”.(24) In acute stroke patients this occurs within 13-48% compared to 10-25% patients in general medical wards.(25)

The main difference between post-stroke delirium - when delirium is occurring alone and not leading to further cognitive decline- and cognitive decline is that delirium is temporary; however the strong links between vascular conditions and the exacerbation these have on any pre-existing dysfunction makes this difficult to distinguish from other common post-stroke cognitive impairments.(25, 26) Furthermore, disruption from stroke leading to delirium has been associated with long-term cognitive impairment. It is thought that delirium may increase the neurodegenerative processes and thus have more than a temporary impact on cognition.(27)

Delirium has three forms: hypoactive/hypoalert, hyperactive/hyperalert and a mix of these syndromes.(28) Different symptoms are associated with each. Hypoactive (most common post-stroke)(28) corresponds with: facial inexpression, motor retardation, speech retardation, decreased reactions, perplexity and mental slowness. In patients with hyperactive type delirium: increased and incoherent talking (logorrhoea), aggression, motor hyperactivity, increased reactivity and delusions are common.(29) Mixed delirium presents with a combination of hypo/hyperactive symptoms or signs with no clear pattern described.(30, 31)

Delirium is not only associated with increased negative outcomes (including: poor functional outcome, time in inpatient care, increased risk of mortality and medical complications)(25, 32, 33) but can also be the beginning of developing/underlying dementia(26) and cognitive decline(34, 35) in some patients.

1.2.2. Vascular cognitive impairment

Vascular Cognitive Impairment (VCI) is a term used to group the variety of cognitive impairments that occur due to vascular abnormalities.(22) Common types of VCI post-stroke include: Post-stroke cognitive impairment (any deficit in any cognitive domain following a stroke)(36); post-stroke dementia (the development of any type of dementia after having a stroke) including Alzheimer's, multi-infarct and mixed dementias (36); and vascular cognitive impairment with or without dementia (cognitive decline in the context of any cranial vascular abnormalities).(37) The level of cognitive impairment post-stroke varies between individuals, stroke type and domains.(14, 17, 38) With severe impairments the risk for developing dementia increases.

1.2.3. Mild cognitive impairment

Mild cognitive impairment (MCI) is a syndrome where “cognitive decline is greater than expected for an individual's age and education level but does not interfere notably with activities of daily life”.(39) MCI can impair a variety of domains.(16, 40, 41) There are two subtypes that have been described: amnesic and non amnesic(42). These are cognitive impairments that either affect or spare the memory domain. Each of these subtypes can also affect a single or multiple cognitive domains.(42) The criteria for diagnosis include: individual and others noticing memory loss (in the presence of amnesic MCI), no other area of cognitive function with apparent impairment, able to be independent in daily activities, no other medical condition that could be underlying memory loss, do not meet the criteria for dementia.(43-45)

People who develop MCI are more likely to have cerebrovascular problems.(46) Those with MCI are at risk of progressing in cognitive decline and developing dementia. Annually, 9.6% progressed to dementia(47), between 8.1 and 8.3% to Alzheimer's Dementia (47, 48), 1.9% to vascular dementia(47) within clinical

settings (e.g. memory clinics). This decreased to 4.9%, 6.8% and 1.6% respectively within community settings.(47)

1.2.4. Dementia

Dementia differs from MCI by dysfunction affecting several cognitive domains more severely and impairs daily functioning reducing the individuals' independence.(39)

Dementia prevalence within the population is high, which could be due to an aging population, but the majority affected are in under-developed countries.(49) In 2005, 24.3 million were diagnosed with a form of dementia and this is expected to double every 20 years.(50) Recent global estimates suggest an overall increase in incidence.(49) However, there is some evidence suggesting that annual prevalence may have begun to decrease within England and Wales.(51) This discrepancy could be due to the improvement of early life education and health explanatory factors as well as an aging population living longer.(49, 51)

Dementia contributes to 11.2% of disabilities in the over 60s.(52) The prevalence of post-stroke dementia varies across different settings: around 30% in the community and 6-32% in hospitals.(17) In patients who are experiencing their first stroke, around 10% develop dementia with this increasing to one in three patients who suffer from recurrent strokes.(53)

1.2.4.1. Pathology of dementia

There are many types of dementia, each with different characteristics and causes: Alzheimer's disease, vascular dementia, other degenerative cause dementia, mixed dementia. The most common subtypes are Alzheimer's disease (54% of all causes of dementia) and vascular dementia (16%).(54)

Alzheimer's disease dementia (AD) is characterised by the presence of plaques in the brain.(55, 56) Research suggests that the presence of these causes irreversible neurodegeneration.(57-60)

Vascular dementia brings about cognitive decline through the lack of blood flow from the cerebral arteries.(61) Unlike AD, vascular dementia does not follow specific neuroanatomical patterns(62). However, it is thought that cerebrovascular ischemia may provoke the production of precursors (proteins that bring on formation of plaques) of AD in the ischemic areas.(63)

1.2.4.2. Risk factors for dementia

The main independent risk factors for Alzheimer's dementia are; apolipoprotein E (ApoE), increasing age, sex (higher risk in females), smoking, diabetes mellitus, vascular disease, hypertension, head trauma, low educational level and (in certain parts of the world) exposure to chemicals such as fertilizers and pesticides.(61)

Risk factors for vascular dementia are; history of cerebrovascular disorders, stroke, hypertension, diabetes, high levels of low-density lipoproteins, smoking, cerebral white matter lesions, exposure to chemicals, alcohol and genetic diseases.(61, 63) Although there are some differences in risk factors between Alzheimer's and vascular dementia, there is also a large level of overlap of risk factors that is reflected in the similar pathology.(60,62)

There is also some evidence for a relationship between depression and development of dementia but the underlying process is unclear.(64, 65)

1.3. Impact of cognition on stroke recovery

1.3.1. Cognitive impact on physical ability

Patients with attention or global cognitive deficits have more severe functional disabilities than those with isolated memory impairments(66) and have a significantly reduced ability to recover even when cognition itself does not feature in the activity performance.(67) Furthermore, cognitive abilities on entering rehabilitation services have a significant positive correlation to end of rehabilitation functional outcome and are negatively correlated both with the length of stay in services(68) and independent living.(14) Specifically, it is the 'higher order' cognitive abilities (comprehension, judgement, short term verbal memory and abstract thinking) that generally seem to have a larger influence when determining the length of stay in services, referral to outpatient therapies and use of therapies at home post discharge.(69) There is also evidence that comprehension levels impact on walking ability.(70) Attention deficits have also been found negatively to affect performance of daily activities and social interactions.(71) Problems with attention are also related to higher levels of accidents and falls.(72)

1.3.2. Domain differences and changes

1.3.2.1. Timing

Research has shown that various cognitive domains are affected depending on the area of the cortex damaged and the time after the stroke.(15, 73, 74) At the acute stage (<1 month) common areas affected are: executive function (particularly speed and attention, 72%)(15); visuo-perception/construction and numerical ability, affecting approximately 34-39%; 30-38% and 30%, respectively.(15, 74) Recognition memory is the least affected area overall.(75)

Attention and speed of information processing are the most prominent impairments. They affect performance in all other domains, which may give false representations of the patient's true capabilities. Under assessment time

constraints, 70% of patients have difficulties and this is reduced to 50% when timing is no longer a factor.(75)

Post-stroke impairments, however, are not stable in severity or expression. Patients between acute stage and 3 months post-stroke show significant improvement across executive functions especially within: speed and attention (number of patients with impairment halved); numerical ability and perception.(15) Transient impairments are most prevalent in the first week post-stroke (39%) compared with after this week (19%).(76) The dynamic nature of post stroke impairments can be illustrated by visual and verbal memory impairments compared to speed and attention. Generally visual and verbal memory are at a lower level of severity than other impairments at the acute stage but unlike other deficits, they do not improve over the first 3 months.(15) For speed and attention impairments improve rapidly over the first few months post stroke are the most persistent; more patients have impairment in this area after 3 months despite rapidly improving over the first few months.(15)

There is some evidence of cognitive impairment stabilising from 3 months to at least 2 years post-stroke: those that have no/some/vast impairment generally maintain this level with few improving or declining.(73) This suggests that if we can predict a patient's stabilised outcome from screening or acute assessments, then a patient's long-term cognitive outcome could be identified and management adapted during the acute stage. However, there is a lack of research into domain impairment stabilisation thus our understanding of post-stroke impairments must improve before this goal can be achieved.

1.3.2.2. Classification of impairment

As mentioned before, there is a lot of overlap between the subtypes of cognitive impairment. Vascular cognitive impairment (VCI) and Vascular Dementia (VaD) both affect the majority of cognitive domains (less impact on verbal retention).(77, 78) Frequencies of impairment across domains (in descending order) include:

information processing speed, praxis-gnosis, visual memory, mental flexibility, abstraction, attention and visuo-construction. They are distinguished by severity and level of impairment present within each population, measured using neuropsychological batteries and other cognitive domain specific assessments. Key distinguishing areas are attention and concentration. In order to classify patients into impaired (VaD or VCI) and no cognitive impairment (NCI), domains including abstraction, mental flexibility, processing speed and working memory are compared. Using these domains 84% of patients can be correctly classified into impaired (VaD and VCI) or NCI groups.(78) The important component that can correctly distinguish 76.6% (of the VCI sub domain) of VaD patients is the severity of concentration impairment.(78)

1.4. Impact of stroke on mood

1.4.1. Mood changes associated with stroke

Mood responses associated with stroke include anxiety(18), depression(79, 80), emotionalism (unprovoked, unfitting and uncontrollable emotional response), catastrophic reaction (inability to complete tasks or feeling inappropriately pressured during a task) and indifference (characterised by apathy and a lack of motivation).(81, 82) At the acute stage, post-stroke major depression is estimated to occur in 25% of patients.(83) Studies show the prevalence of depression and anxiety symptoms post-stroke is high(79) and negatively impacts on mortality and recovery.(84-86) However, it is important to draw a distinction between depressive or anxiety symptoms (found for example on a psychometric mood scale such as HADS) and a clinical diagnosis of anxiety or depression. These are not the same and arguably, some prevalence studies may over estimate the prevalence of depression (the clinical syndrome) by conflating it with the presence of depressive symptoms.

In a recent systematic review of the incidence and prevalence of post-stroke mood problems, pooled analysis suggested that at anytime post-stroke prevalence was about 29% and was stable overall within ten years post-stroke. There was no

significant difference found in prevalence across the various stages post-stroke: up to one month 28%; one to six months 31%; six months to a year 33%; and over one year 25%. Prevalence also was not significantly different depending on the setting. Hospital and rehabilitation settings post-stroke each had a prevalence of 30% and community settings only 22%. From pooled analysis, depression incidence post-stroke within the first 5 years varied from 39% to 52%. There was significant heterogeneity across study findings but this demonstrated the instability of development and recovery from depression.(87)

Although poorly researched in comparison, anxiety is thought to occur between 4-28%(88) and 3% for adjustment disorder.(89)

Pooled prevalence of any type of anxiety disorder after stroke is 20%. At the acute stage anxiety prevalence is 20% versus 23% up to five months and 24% from six months and after stroke. Like depression, there is a slight variation in prevalence across different settings: 25% in hospitals, 21% in rehabilitation and 22% within the community.(90) Compared to general hospital inpatients, mood disorders are higher in stroke cohorts.(91, 92)

The most common types of anxiety disorders post-stroke are phobias and generalised anxiety disorders. There is however, no significant difference in anxiety prevalence between patients suffering from first ever stroke and recurrent stroke.(90)

Another common symptom is fatigue. This is defined as “a sense of exhaustion, lack of perceived energy or tiredness that is distinct from sadness or weakness”.(93) This occurs in around 24% of stroke survivors at the acute stage (within the first few weeks) post-stroke.(93) There is a lot of overlap between these emotional responses, which increases the difficulty of distinguishing each affect in terms of epidemiology and impact on recovery, in both the long and short term.(81, 94)

1.4.1.1. Depression

There are predisposing factors that make stroke patients more susceptible to developing depression and for it to be maintained at one year post-stroke. These include a previous history of depression, prior strokes, impairment in communication, low level of functional independence, perceived stress, low levels of reasoning capability and a low level of internal locus of control (the belief that the individual has control over what happens in life events).(20, 95-98)

Other factors that can predict post-stroke depression at any stage include: post-stroke disability, pre-stroke history of depression, cognitive impairment, stroke severity, anxiety and a lack of support from family or social circle.(87)

There is also some evidence that suggests that ischemic strokes in the left hemisphere increase the possibility of depression with cognitive impairment, which increases the persistence of the depression compared to depression alone.(99, 100)

Early neuroimaging studies suggested a relationship between stroke lesion location and mood disorder. Subsequent reviews have found significant heterogeneity among lesion study findings. Overall, there was no significant association between lesion location and development of PSD in all type depression, major depression or various depression types within the first month post stroke.(87, 101)

1.4.1.2. Emotionalism

Post-stroke Emotionalism (PSE) is characterised by an “increase in the frequency of crying or laughing episodes” compared to the pre-stroke state of the patient. It is characterised by having a sudden onset, with the emotions feeling like they are beyond the patient’s control.(82) PSE has now been described as being on a continuum with two main levels of severity. The first is pathological laughter and crying (PLC). Brought about through emotionally nonspecific stimuli, it has no effect on patients’ mood after the episode of laughter or crying. The patient does however lose control of their facial expressions during an episode. The less severe

end of the continuum is emotional lability (EL). Unlike PLC, this is triggered through stimuli that have an emotional context. Feelings and expression are also experienced as unexpected and uncontrollable. EL however, can affect the patient's mood after an episode.(102)

The prevalence of PSE in stroke survivors is between 10 and 20%. PSE has a large overlap with post-stroke depression (PSD) with between 30-50% of PSE patients also suffering from PSD.(103) The difference is that PSE is a 'dysfunctional expression of emotion' and depression an 'abnormal formulation of emotion'.(103) In addition PSD has been shown to decrease over the first 3 months post-stroke and PSE increases in prevalence.(104) Nevertheless, unlike PSD, PSE has some evidence that significantly relates occurrence to lesion location. The evidence suggests that microbleeds in the anterior and paramedian regions of the thalamus lead to a poor thalamofrontal connection which is the route of the out of control feelings and emotional symptoms.(105) As it is well known that executive functions (such as emotional control) are mainly within the frontal regions of the cortex, PSE has been found to correlate with microbleeds in the frontal cortex alongside executive function impairment.(106, 107) This again supports the idea that emotional problems likely have a strong association with cognitive impairments.

1.4.1.3. Anxiety

Post-stroke anxiety, like depression, is common in community dwelling stroke survivors, especially in younger patients with a lower level of education.(108) Around 30% of patients are in the borderline category (above normal range but below cut-off for a problem) and 16% reported as having anxiety problems.(108) There is a high level of co-morbidity between PSD and post-stroke anxiety (PSA).(88) It is therefore difficult to distinguish the factors that put patients at risk of anxiety alone. PSA is less well researched than PSD, but it is also known to impact on quality of life(109) and engagement with rehabilitation.(110) Patients debilitated by uncontrollable worry may avoid physical therapy sessions for fear of

failure (due to setting themselves unrealistic goals)(111) and/or falling.(112) Fear of stroke recurrence can be a further problem.(113)

However, some evidence has been found comparing characteristics of stroke patients with various levels of worry and anxiety with and without depression. The results suggest that unlike depression, anxiety is not as vulnerable to the patients' background or stroke severity but the structures damaged by the stroke. These tend to be more posterior than depression related lesion areas.(114) A common anxiety disorder in stroke (Generalised Anxiety Disorder) has been found to be associated with lesions in the right hemisphere and the left when co-morbid hemisphere with depression.(115-117) However, as previously mentioned for PSD, there are mixed findings in relation to mood disorders and lesion location. There may be a significant relationship between anxiety and depression and the location of the lesion. However, the heterogeneity within mood assessment methods, research design and patient demographics suggests this relationship requires further work to be established.(118)

1.4.1.4. Adjustment disorder

Stroke not only leads to disruptions in mood, it can also be difficult for stroke survivors to accept and come to terms with the disabilities they have been left with and how this now impacts on their way of living.(119) Adjustment is: "the process of adaptation that occurs over time as the individual manages, learns from and accommodates the multiple changes which have been precipitated by changed circumstances in their lives".(120) Adjustment disorder is defined by the DSM-IV as "marked distress that is in excess of what would be expected given the nature of the stressor or by significant impairment in social or occupational functioning"(121) It can be acute (symptoms resolving within 6 months of the stressful trigger) or chronic (symptoms persisting past 6 months).(122) In an adult (non-stroke) psychiatric population, occurrence is between 5 and 21%.(123) Depending on the difficulties the patient encounters, the adjustment process has to be flexible, especially in stroke survivors where there is a wide variety of severity and type of

challenges to cope with.(119, 124) Stroke survivors with aphasia have described obstacles such as: the impairment itself, how they feel, isolated from others, inaccessibility to help and poor knowledge of their condition. The strategies in which these are challenged include: new ways of communication, interacting and sharing experiences with others in similar situations, help provided to make interacting easier as well as information on their disability and how to feel more in control.(125)

For stroke patients in general, there are four main themes that contribute to adjustment. These are: personal attributes (determination, perseverance, positive attitude, hopefulness and inner strength); adjustment strategies which are either practical (adapting activities, relearning old skills, goal setting) or mental (considering alternatives i.e. “what could have happened”); social support combining practical, emotional or moral help; and environmental changes such as structural modifications of home to accommodate for disability, provision of health care either locally or directly to home.(124)

Before a patient adjusts to their new situation, coping strategies can either be unhelpful or beneficial. Unhelpful or negatively orientated techniques include: avoiding situations, worrying, fantasising that things will be different, thinking that it is their fault and inappropriate use of harmful substances such as drugs or alcohol. These cause the patient to experience higher levels of anxiety, depression, dysfunctional thinking as well as impacting negatively on their self-esteem.(126) Beneficial methods are the individual being proactive in finding solutions to the problem(s), ability to successfully manage stress through finding the funny side of situations and getting involved in activities. This approach tends to be implemented by those with a higher level of self-esteem and pre-stroke intelligence.(126) Coping strategies are linked to adjustment, which suggests that adjustment is improved with fewer maladaptive coping strategies.(126, 127) A cohort of acquired brain injury patients demonstrated this. Through a significant increase of adaptive coping strategies (seeking support and cognitive processes to adapt), patients showed a significant decline in depressive symptoms and an increase in reaching goals of therapy.(128)

1.4.1.5. Fatigue

As described previously, post-stroke fatigue (PSF) is a subjective feeling of tiredness and exhaustion. It can be brought about in relation to maintaining effort for a task, poor motivation or lack of effectiveness in performance.(129) Like cognitive impairment, fatigue prevalence varies with post-stroke timing. Overall prevalence across all times is between 30-72% of stroke survivors.(129-133) It has been shown to be a persistent and relatively stable problem after stroke, with around 30% having PSF at 6 months and 34% one year after stroke.(134) There is a strong association between PSF, PSD and PSA at one year post-stroke.(134, 135) This association suggests it might be possible that PSD, PSA and PSF could contribute to maintaining each other, however association of such variables does not imply any causality.(131, 134) The converse relationship has also been described, with depression influencing the effect that fatigue had on physical ability.(132) However, this may only be true for some stroke survivors. The relationship between fatigue and mood may be even more complex, one review found that although severe fatigue is regularly interpreted as a sign of depression, only a small proportion of these patients have higher depression assessment scores. In addition, depressive symptom variance in patient groups was explained by lack of physical activity.(133)

Fatigue also negatively affects post-stroke recovery in the long and short term. PSF is linked to; cognitive impairment especially in attention and executive function domains(134), feeling of loss of control(135), speech impairments, feeling of poor health, attendance or living in a rehabilitation centre, low level of independence in activities of daily living and an increased mortality rate after 3 years.(131) These effects are likely to have a reciprocal relationship with a low mood(129, 136) and overall poor outcome i.e. feeling unwell will prevent or reduce attempts at activities of daily living independently.(131, 135)

Characteristics that have been shown to predispose stroke survivors to PSF include: older adults, low levels of self motivation, pre-stroke rehabilitation care, pre-stroke dependency on activities of daily living as well as prior stroke history.(131)

1.4.2. Effect of mood on stroke outcomes

PSD and PSA lead to an increase in mortality. Patients with PSD have been found to be three times higher chance of mortality within ten years post stroke than non depressed survivors independent of other risk factors.(137) There is a high risk of suicide with stroke cohorts making up 7.2% of annual incidence of all suicides in one area of a community sample(138) and a significant association between higher ratings of depressed mood and mortality at 12 and 24 months post-stroke.(139) Although suicide is an important aspect as it is potentially preventable, in absolute numbers, suicide as a cause of death in stroke has modest effects.

Quality of life(109, 140) and engagement with rehabilitation are also affected.(110) Anxiety is also associated the level of pain a patient is in, their emotional reaction, ability to sleep as well as how socially isolated they become. Co-morbid anxiety and depression are related to a decline in energy levels thus making it harder for patients to benefit from interventions (140) and have the motivation to participate in physical activities and engage with others.(141) PSE has also been found to be associated with features of distress, negative psychological states and relationships which affect quality of life post-stroke.(142)

Furthermore PSD present while the patient is within hospital settings negatively impairs activities of daily living. Although functional abilities improve after depression is treated (143), patients who suffered from depression have a slower rate of recovery even after PSD has depleted. These effects have been found up to two years post stroke.(144) Low levels of functional outcome at 15 months post stroke are independently related to depression at 3 months post-stroke but this relationship is not present when using physical ability at 3 months to relate to depression status at 15 months.(145)

1.5. Assessing cognition and mood impairment in stroke survivors

Stroke survivors with cognitive or mood deficits may have better outcomes if diagnosis is made at an early stage and appropriate management is started promptly (67, 146). A recent national priority setting exercise identified “psychological problems” (particularly cognitive impairment and depression) as the most important but under-researched issues for stroke survivors and carers.(147) As they have potential effects on all aspects of function, some have argued that cognitive measures themselves may be a useful “global outcome” measure for stroke trials.(148) The gold standard for diagnosis of clinically significant cognitive impairment is measured through a detailed neuropsychological battery and a structured psychological interview for mood disorders. The gold standard for dementia is a clinical diagnosis using the DSM-IV criteria. These vary depending on the subtype but the two most common are vascular and Alzheimer’s dementia. Vascular dementia is diagnosed if the following are met:(121)

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:
 - (a) Aphasia (language disturbance)
 - (b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) Agnosia (failure to recognize or identify objects despite intact sensory function)
 - (d) Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities,

weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during the course of a delirium.

The patient is diagnosed with Alzheimer's disease dementia the following criteria are met:

A. The development of multiple cognitive deficits manifested by both

(1) Memory impairment (impaired ability to learn new information or to recall previously learned information)

(2) One (or more) of the following cognitive disturbances:

- (a) Aphasia (language disturbance)
- (b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
- (c) Agnosia (failure to recognize or identify objects despite intact sensory function)
- (d) Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

- (1) Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumour)
- (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
- (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Episode, Schizophrenia).

These are time consuming and stretch the already limited resources of psychological services. Therefore, the use of accurate screening tests is the best strategy to be employed in an attempt to reduce such a burden and implement early intervention. UK national dementia strategy emphasises the need for good quality, early diagnosis to facilitate evidence based intervention and discussions around management and prognosis. However, many people with dementia remain undiagnosed or are diagnosed late in their disease journey. The importance of cognition and mood is recognised in International guidelines, where routine assessment is recommended for all stroke survivors but no direction is offered as to the preferred strategy.(149, 150) Despite the importance of measurement of these areas post-stroke, there are arguments that screening may be causing more harm than good. Without evidence for effective interventions screening may overwhelm psychological and other services as well as cause distress to patients and family.(151, 152) This is discussed in more detail later.

In clinical stroke trials, outcomes are usually based around domains of: physical function; quality of life and mortality.(153) There is however potential benefit in including cognitive/mood assessments in trials. For intervention trials, stroke survivors with substantial cognitive or mood deficits are often excluded. However, lesser problems with mood and cognition may still impact on activity and participation outcomes.

1.5.1. Assessments

Health professionals have developed many tools to measure both cognition (with its' various domains) and mood. Despite having tools developed specifically for use in stroke, these are not regularly administered.(154) Instead, measurement choice is based on the popular clinical assessments used in unselected older adults and on opinion and preference of the health professional. There is a large overlap in

assessments chosen for the older adults, those with suspected dementia and those suggested for stroke patients.(22, 49, 51)

Assessments can be directly administered to the patient or indirectly to a proxy (usually a family member or caregiver). Depending on the assessment, timing and the intended impairment to be measured the choice of available tool differs. In patients with frontal temporal dementia (FTD) and AD, indirect assessments appear to be better at quantifying the capability of patients' day-to-day independence.(155) However, in general, proxy assessments of patients' are not always valid. For example, proxy measured patient quality of life had poor correlation with other measures (proxy estimates of health related quality of life scales, the Health Utilities Index) when assessed early post-stroke.(156) This finding was similar in a study of pain reporting in cognitively impaired children. Parents tended to overestimate pain levels of their child early on.(157) The variations in proxy assessment validity could be because of the potential temporary impairments of stroke patients, or stress, anxiety and getting used to changes caused by the stroke that the proxy might experience affecting judgement of patient ability. In light of this, we would assume that direct assessment would be more accurate in the early stages, using indirect assessments for severe cognitive impairments that have developed or changed over a reasonable amount of time.

Below I describe some of the direct and indirect tools administered in both hospital and community settings for testing cognition and mood.

1.5.1.1. Cognitive assessments

Selection of cognitive assessment tends to be based around time required for completion, patient burden and requirement for specialist training. Popular assessments include:

1. Folstein's Mini Mental State Examination (MMSE)

The MMSE is a short 30 point questionnaire to screen and grade cognitive impairment. It was developed to replace lengthy batteries with a shorter more efficient assessment.(158) It has 6 sections that include; orientation, registration, attention and calculation, recall, language and commands. It is scored out of 30 with ≥ 25 being normal, mild between 21-24, moderate 10-20 or ≤ 9 indicating severe impairment. It takes between 5-10 minutes to administer.(158) MMSE has been used in several seminal research papers.(22) Copyright is now being enforced and continued use of the MMSE has financial implications. The MMSE demonstrates good sensitivity to correctly identify people with suspected dementia in specialised settings. However it does not show the same capabilities for diagnosing MCI and AD, or distinguishing one from the other. Furthermore, the components of the MMSE are unable to provide a measure of executive function.(159) For these reasons many centres are exploring, and are recommended to seek, alternative screening tools.(160)

2. Montreal Cognitive Assessment (MoCA)

The MoCA was originally developed as a brief screening tool to identify older adults with MCI that score in 'normal range' on other commonly used assessments.(161) MoCA has many properties that make it attractive for use with stroke survivors, however normative data are derived from community dwelling older adults and traditional MoCA score cut-offs were designed to distinguish mild cognitive impairment.(162) It is a 30-point test (≥ 26 is normal), taking about 10 minutes to complete. It assesses several domains; short-term memory-recall; visuospatial ability; executive functions; language and orientation. It is recommended for use in stroke by specialist societies.(22)

There are mixed reports regarding validity of the MMSE and MoCA in identifying post-stroke cognitive impairments depending on the setting.(138, 163) Despite the MoCA having a higher sensitivity than the MMSE overall, they both appear to be equally as efficient at identifying impairment at the acute stage post-stroke.(164, 165) However, there is an argument that with a change of cut-off, the MoCA is the

better choice of test as the MMSE is highly focussed towards orientation rather than executive function which, as previously discussed, are the telling areas of functionally debilitating cognitive impairment.(154, 166)

3. Adenbrookes' Cognitive Examination -Revised (ACE-R)

The ACE-R was developed to fulfil the need for a bedside assessment that would diagnose and differentiate AD and other dementias, especially FTD. It encompasses items that assess the key cognitive domains involved in AD and FTD not included in other measures without the use of expensive clinical equipment. As the MMSE is widely used and validated as a brief mental status assessment, it was included within the ACE-R.(167) The ACE-R was validated as a good screening tool for cognitive impairment in rehabilitation settings of brain injury patients(155) and the language component appropriate to assess for aphasia in non-acute post-stroke patients(168) and some cognitive domains (i.e. visuospatial, attention and executive function) in acute stroke patients.(169) In post-acute stroke, the ACE-R is an effective tool to identify mild cognitive impairment.(166) Nevertheless, it has been found to be inappropriate for acute screening for overall cognitive impairment post-stroke due to confounding factors of acute stroke affecting performance on a lengthy and complex assessment.(169) There is however, a lack of research into the use and validity of the ACE-R post stroke.

Due to the changes in copyright with MMSE a revised ACE the ACE-III has been developed. ACE-III includes items similar to the MMSE but does not allow for a full MMSE score to be calculated. Like the ACE-R, ACE-III is still scored out of 100 and assesses five domains: orientation/attention (out of 18), verbal fluency (14), memory (26), language (26) and visuospatial function (16).(168, 170) Research has shown that the ACE-R can differentiate between AD and FTD and organic brain disease vs. psychiatric states.(171) Therefore, it is suggestive that the ACE-III will be able to do the same. The ACE-R cut-off values vary in accuracy and validity; <88 gives 94% sensitivity and 89% specificity and <82 gives 84% sensitivity and 100% specificity for dementia within community samples.(167) The same cut-off points

will be applied to the ACE-III. Despite the ACE-III showing high sensitivity and specificity,(172) it takes around 30 minutes to complete in the general population and likely longer in stroke cohorts due to other impairments. Stroke patients, as mentioned previously, have poor attention and concentration as well as reduced cognitive processing speed. These alongside any other physical or speech impairments are likely to result in the patient struggling to complete the assessment.

4. Hodkinson's Mental Test and Abbreviated Mental Test (AMT)

The AMT is a 26 item direct patient assessment. It was developed to measure cognitive impairment in the elderly population.(173) Shortened versions, the AMT-10(173) and AMT-4(174, 175), have been developed to further reduce clinician and patient burden. Questions are a combination of orientation, recognition, memory and attention domains. Dementia screening tests are preferred that do not require reading, writing, drawing and do not rely on a certain education level(176) which is something that the AMT provides. It has been validated for detecting cognitive impairment across community and hospital populations.(177-179) However, although the AMT is validated across patient cohorts and is quick to complete, it is very heavily focussed on orientation and relies on verbal responses. Thus it is unlikely to be suitable for many patients with aphasia.(180)

5. Confusion Assessment Method (CAM)

The Confusion Assessment Method (CAM) is the most commonly used delirium assessment system and has been validated for use in hospital inpatients.(181) The CAM is a two part clinical questionnaire to screen for delirium. A main advantage of this assessment is that it requires little formal training in comparison to other delirium assessments.(44) The first section contains 11 items that assesses overall cognitive impairment: acute onset; inattention - presence and abnormality; disorganised thinking; altered level of consciousness; disorientation; memory

impairment; perceptual disturbances; psychomotor agitation and retardation; altered sleep-wake cycle. The second section comprises of four main features found to distinguish delirium from other cognitive impairments: acute onset and fluctuation course; inattention; disorganised thinking; altered level of consciousness. Diagnosis of delirium is the presence of the first two features plus one of the others.(182) It takes around 5 minutes to administer.

Although the CAM has not been specifically validated in acute stroke cohorts, it has been validated to identify delirium within ‘critically ill’ hospitalised patients. Moreover, the CAM-ICU format has been validated in post-stroke patients within intensive care units.(157, 183) It is therefore limited in identifying global cognitive impairment.

6. Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE)

The Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) is a questionnaire filled out by a caregiver/relative to determine the cognitive status of the person in question. It assesses change in ability as a screen for cognitive decline or dementia. It has 26 or 16 items relating to everyday tasks. The informant has to rate the person in question in each task from 1 (much improved) to 5 (much worse).(184) It takes about 5 minutes to complete.

The IQCODE has had mixed reviews in detecting post-stroke dementia(185, 186), but has been suggested to be used as supplementary information to complement patient based clinical assessments.(156, 187) It has, however, been recommended and used as a good measure of pre-morbid stroke cognitive status(188, 189) and correlated with other cognitive assessment that can be administered post-stroke.(190) However, an indirect assessment does not give a true measure of a patient’s performance and may over or under exaggerate a person’s cognitive capabilities.

1.5.1.2. Mood assessments

Mood assessments are generally self-reporting questionnaires that rate feelings over a recent period of time. Again these require usually little training in administration. The favoured mood assessments include:

1. *The Centre for Epidemiologic Studies Depression Scale (CES-D)*

The CES-D assesses depressive symptoms over the previous week using negatively and positively phrased statements about behaviour and feelings.(191) It is a self-report questionnaire that was designed for use in the community. There are 20 phrases scored on a likert scale of how often they have experienced this statement (rarely or none of the time - less than 1 day to most or all of the time - 5 to 7 days), each is rated 0-3. There are 4 positively phrased statements, which are scored backwards in their regularity of occurrence. Higher scores are representative of a lower mood. There are 9 areas of symptoms covered by the questionnaire. These include: sadness, loss of interest, appetite, sleep, thinking or concentration, guilt, tiredness, movement and suicidal ideation. The categories for depression are based on the cut-offs: less than 16 for low depression, 16-25 for mild depression and 26 and over for major depression.(48) It has been validated in community (60, 70, 192) and stroke populations.(193-196)

2. *Hospital Anxiety and Depression Scale (HADS)*

HADS(197) is a validated screen for depression and anxiety in acute hospital settings and stroke (198, 199), reports of accuracy are mixed.(200-202) HADS comprises 14 multiple-choice items (7 for depression and 7 for anxiety) each scored 0-3 giving a total score of 42 (21 per subscale). HADS is designed to not be influenced by somatic problems. This is achieved through items relating more to feelings of enjoyment towards activities rather than physical ability, and avoidance of items relating to somatic symptoms of medical illnesses e.g. insomnia or fatigue. This design means HADS is not influenced by somatic problems, making it more suitable as a mood symptom screen for all types of physically impaired or ill patients.(198) HADS can be administered verbally. Conventional scoring defines “definite

abnormal mood” as HADS \geq 11/21 for each subscale; scores of 8-10 are “possible abnormal mood”. However, it has been suggested that in stroke cohorts cut points should be lowered to improve accuracy especially in cases where there are communication problems.(51, 201, 203) Cut-offs as low as >4 or >5 have been found to be reasonable in detecting mood problems.(202, 204) Although, when a higher cut off for depression subscale (\geq 7 or \geq 8) and lower for anxiety (\geq 5 or \geq 7) is implemented, accuracy increases.(49, 199)

3. Geriatric Depression Scale (GDS)

The GDS was developed specifically for screening an older adult population for depression. There are 3 versions of GDS: 30, 15 and 4 point scales.(71) The 30-point version of the scale has been validated in stroke cohorts but research suggests it is likely to require a complementary, more specific instrument used in tandem (i.e. Becks Depression Inventory).(193, 205, 206) It is a self-rating questionnaire comprising of 30 statements about feelings over the past week with a binary answer (yes or no) for each. The statements are phrased in a positive or negative way with the corresponding ‘depressive’ answer representing 1 point. Scored out of 30, normal range is considered between 0 to 9 (inclusive), mildly depressed between 10 to 19 (inclusive) and very depressed 20 to 30.(71) This has been validated in hospital populations(207) and as a shorter version.(72)

The CES-D, HADS and GDS all require a certain degree of concentration in order to process and choose a response to a multiple choice answer. Stroke patients with poor attention may struggle even when supported and the scales are verbally administered. Furthermore, each scale likely requires a degree of intact executive function. As there is a high proportion of cognitive impairment within stroke patients, especially with executive function, responses to such scales could be affected and thus may provide a less than accurate assessment of mood symptom presence. Simplified measures such as DISCS and Yale Single Question may be more appropriate.(208, 209)

1.5.2. Identification of post-stroke cognitive and mood impairment

Before an abnormality can be treated we require a clear way of identifying it.(210) By gathering information on abnormalities across patients, disorders can be described and defined. In order for disorders to be identified, an accurate form of assessment is needed. Health professionals require tools that can distinguish presence or absence of a disease before an intervention can be attempted.(211, 212)

Assessment in the first few days after stroke may be complicated by impairments of communication, physical function and medical illness. Aphasia, common in stroke(213), can lead to depression post-stroke(96) but also can limit measures used and provide inaccurate diagnosis.(214, 215) Stroke severity and resulting physical impairment may complicate assessments that require motor skills. Stroke severity (motor impairment) is related to depression(216, 217) and likely to be related to anxiety(218).

In order to decide what is and is not a good identifier, statistical measures are used to describe the capability of the measurement tool and compare it against others. Assessments are generally compared to the best way of identifying the disease, also known as the 'reference standard', to determine test accuracy.(219)

1.5.3. Precision

Commonly used clinical accuracy descriptors are: sensitivity, specificity, likelihood ratios and predictive values. These relate to the probability and performance of the assessment being analysed (index test) giving a correct disease positive or disease negative classification base on the reference standard outcome and disease prevalence.(211)

Sensitivity is a measure of the assessment ability to identify subjects with a specified disease. In other words it is the probability of the subject getting a

positive index test result when they have the disease in question. Specificity complements sensitivity in that it describes the proportion of subjects that get a negative index test result that do not have the disease in all of those without the disease in the cohort being assessed. It is the probability that a negative test result will be found in a non-diseased subject.(220) There is generally a trade off between sensitivity and specificity. If the test involves a graded score then the probabilities associated with sensitivity and specificity can be made to vary depending on the diagnostic threshold. By increasing the threshold, sensitivity decreases and specificity increases and vice versa when threshold is lowered.(221) This is illustrated in Figure 1-2.(211)

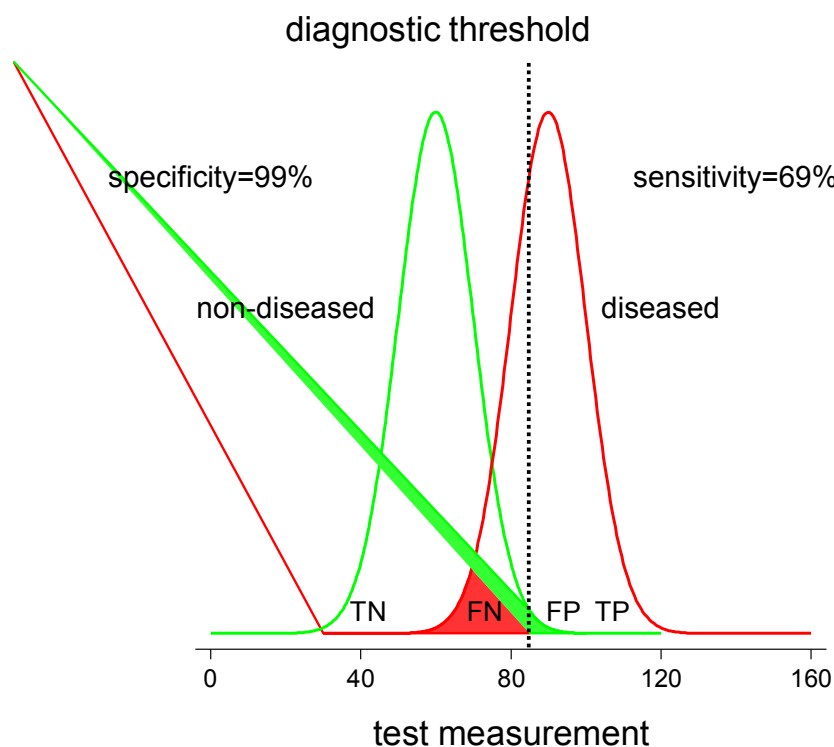


Figure 1-2 Effect of varying diagnostic threshold on test accuracy

Taken from the Cochrane handbook for systematic reviews of diagnostic test accuracy (chapter 10 p12)(211)

Likelihood ratios are the ratio of an expected index test result in those with a disease to those without disease. It links the probability of the subject's pre and post test disease presence i.e. how likely is it that a certain test result will occur in those with or without the disease. There are two different ratios calculated from accuracy data. The first, positive likelihood ratio (LR +), is how likely it is that a positive index test result will occur in a subject with the disease than a subject without. This is usually >1 . Second is the negative likelihood ratio (LR -), which is the ratio of probability that an index negative test result will occur in a diseased subject to the probability that it will occur in a non-diseased subject. Therefore it is how much less likely that a diseased subject will be classified as negative than someone without the disease. This is usually <1 . Each of these ratios are calculated from sensitivity and specificity of the index test: $LR+ = \text{sensitivity}/(1-\text{specificity})$ and $LR- = (1-\text{sensitivity})/\text{specificity}$.(220)

Predictive values, also a measure of accuracy, differ in that they take into account sensitivity and specificity along with the prevalence of the disease. The positive predictive value (PPV) is the proportion of patients that have a positive index test result in the total number of subjects with the disease i.e. the probability that a positive test result will be in a subject with the disease. Negative predictive value (NPV) is the opposite, the probability that subjects without the disease will have a negative test result. These probabilities are dependent on the prevalence of the disease within the cohort being tested i.e. in a population with a high prevalence of the disease will have a high PPV and low NPV.(220)

Calculation of these measures are illustrated through a 2x2 table.(127, 183) (Table 1-1).

Table 1-1 2X2 table to calculate sensitivity and specificity

		REFERENCE STANDARD		
INDEX TEST		Disease Present	Disease Not Present	
	Test Positive	True Positive (TP)	False Positive (FP)	PPV $TP/(TP+FP)$
	Test Negative	False Negative (FN)	True Negative (TN)	NPV $TN/(FN+TN)$
		Sensitivity $TP/(TP+FN)$	Specificity $TN/(FP+TN)$	

PPV= Positive Predictive Value, NPV= Negative Predictive Value

From the 2x2 table the positive and negative predictive values can also be calculated. These are probability calculations. They measure the probability that a positive or negative disease outcome on the index test is a true positive or negative disease presence. These values are a measure of how well the test can identify those with and without the disease in comparison to the gold standard.(194)

Interpretation of what is good sensitivity/specificity is subjective. In statistics arbitrary values of 'poor' and 'good' sensitivity and specificity have been described, but these values are of limited utility in practice as the threshold at which we define acceptable test accuracy is fundamentally dependent on the clinical meaning of false positive and false negative results.

For example false positives could lead to invasive and painful follow-up procedures if testing for cancer. Unnecessary cancer treatment carries risks. Alternatively, if the patient were given a false negative they would be missing out on potential treatments that they could benefit from. In this work, I am trying to determine if the patient is at risk of dementia or other multiple domain cognitive impairments that could infringe on their recovery post stroke. Unlike my example of cancer, there is a lack of established beneficial treatments or therapies. Mood problems are similar in that not all stroke patients respond well to antidepressants or anti-anxiety medications. Some psychological therapies are available but again vary in effectiveness depending on the patient. However, both cognitive and mood problems can lead to a lack of independence, reduce activities of daily living and thus quality of life.

False positives could inflict psychological distress on the patient and family, generate unnecessary stigma of a mental health diagnosis, increase costs for future planning, incur direct costs and burden from further tests, place strain on relationships and force inappropriate lifestyle changes yet with no guaranteed beneficial treatment. False negatives from screening could prevent the patient from receiving help when it would have the biggest beneficial impact. They would not gain access to educational or supportive resources, would incur increased

financial costs as their condition deteriorates, may become a danger to themselves and or others, and loose the opportunity to plan for implementation of their wishes when they lose capacity to make their own decisions. They also suffer from adjustment issues from being given the wrong information from screening test.

For a measure to be valid it must also be reliable along with accurate. Reliability is defined as 'the ratio of variance of the true values between individuals to the variance of the observed values (combination of individual variation and measurement error)'.(222) An assessment must be able to perform in the same way across a population. There are three overlapping terms that cover assessment reliability. These are: interrater - ability for the assessment to be administered by different people and perform in the same way; intrarater - ability of the assessment to be consistent when administered over several occasions by the same person; test-retest reliability - for the assessment itself to be consistent with measurement when administered to the same patient.(223) Inconsistencies across these can lead to assessment validity decreasing.(224, 225)

Validity describes how well an assessment measures what it claims to test. There are five types of validity: construct validity - does the test assess what it is meant to; concurrent validity - does the assessment correlate with other similar tests overall and in individual components; face validity - if the test seems to measure what it is meant to; localisation validity - does the assessment tap into different domains accurately; ecological validity - can the assessment predict actual capabilities of the individual assessed.(223)

1.5.4. Prognosis

An important component of valid identification of deficits is distinguishing between transient problems and those that have a long-term impact. The most important problems are those that will persist. In addition to cross sectional descriptions of test accuracy (i.e. comparing and index test and gold standard at a single time point) there is an argument for describing ability of a screening test at a certain

time point to predict development or persistence of a problem. This approach is often referred to as delayed verification accuracy.(226) Therefore in screening tools, sensitivity is generally favoured over specificity so that those with a potential issue can be properly assessed after a positive screening result. This discussion is continued in section 1.5.6.

1.5.5. Feasibility and acceptability

In order for problems to be detected the tests not only have to be accurate but able to be administered/completed by the patients. If the assessment cannot be completed by the majority of patients within a certain population then resulting data will be biased.(227) Feasibility can be determined by describing proportions of patients who are able to complete assessments against the total population that would be tested. It can be useful to describe to what extent extra assistance is required to attempt/complete measures. Acceptability can be estimated from those that refused/withdrew compared to those that consented. Potential strategies to improve feasibility and acceptability include explanation of the screening tool by the test administrator(195); protocols in place for when a positive result is found(196); proper training in the use of assessments to improve confidence of the administrator and to reduce assessment time.(200)

1.5.6. Cognitive and mood screening debate

Guidelines recommend that all stroke survivors are assessed for cognitive and mood dysfunction(150, 228, 229) However, lack of evidence for interventions having a positive effect on outcomes questions the benefits of screening measures.(230) It has been argued that early diagnosis with no available effective interventions or treatment for cognitive problems could cause more harm than good, leading to overburdening of medical resources and unnecessary testing.(152) Furthermore there is evidence of negative psychological effects on patients diagnosed with dementia. The diagnosis can lead to patient distress, frustration, anger as well as

affecting close relationships and even increasing the risk of suicide.(231, 232) Research suggests that this issue is more apparent in cognitive screening and not mood.(233)

In order to make recommendations regarding neuropsychological assessments, especially in screening for cognitive impairment, their needs to be development in several areas. Research is required in diverse patient groups to identify the benefits and possible harmful effects of assessment and if this differs between patient cohorts. Investigations into the characteristics and natural development of cognitive impairment and mood problems (e.g. depression and anxiety disorders) is needed to improve our understanding of potential diagnostic benefits as well as development of accurate screening and diagnostic tools across a variety of populations.(234) In clinical practice, if we are to offer screening we must have robust strategies to deal with any potential problems detected by the assessments, this could include training and educated of healthcare staff and improved access to support services.(229, 235)

1.6. Main research aim

This research therefore aims to identify: what, if, when and how cognitive and mood screening can be implemented at certain stages in the stroke patient journey.

A good screening test should: not require specialist training to administer or interpret; be as short as possible to reduce patient burden, administration and interpretation time; have good sensitivity and specificity; be able to be completed by the majority of patients and not vary in performance depending on patient co-morbidities or administrator. I will describe certain of these properties for tools used in stroke research and practice.

I will do so by: identifying the assessments used in research and clinical practice and how valid they are in stroke cohorts; investigating the accuracy of these

commonly used assessments in identifying multi-domain cognitive impairment, dementia and clinically persistent mood problems; determine the feasibility and accuracy of cognitive and mood assessments in the acute stroke stage.

1.7. Research strategy

To investigate these research questions I present a series of projects that follow a common thread to describe cognitive and mood assessments in stroke. I first established the prevalent cognitive and mood assessments in the literature and in usual practice. In establishing common assessments I carried out diagnostic test accuracy reviews and original research of preferred assessments (direct strategies) and describe their test accuracy (sensitivity, specificity). In addition I assessed the feasibility of preferred assessments at the acute stage post- stroke.

I hope that this work will inform treating teams on how to effectively detect clinically important cognitive and mood impairments, overcoming obstacles within the hospital settings and common physical impairments experienced by stroke survivors.

This should allow for the identification of when post-stroke is it possible to screen to provide meaningful information. Through this, I hope to provide the foundation for developing guidance of valid assessment of cognition and mood following stroke.

Chapter 2 Investigation of cognitive and mood assessments used in research and usual practice

2.1. Introduction

As discussed in chapter one, clinical research tends to focus on physical function, quality of life and mortality as main outcomes post-stroke.(153) With cognition and mood impairments impacting on recovery it is important that these are considered in research endpoints to give a more detailed view of patient recovery. With evidence of cognition and mood impacting on all aspects of function, some have argued that cognitive measures themselves may be a useful “global outcome” measure for stroke research.

Many cognitive/mood assessment instruments are available to researchers, but at present there is no consensus on optimal measure(s) for use in stroke practice or research. Literature around the properties of stroke trial assessments is emerging, although to date there has been limited research on the properties of common cognitive/mood assessments in stroke. Screening and assessment tools that are validated and popular in non-stroke settings may not be appropriate in stroke survivors, who are more likely to have language, physical and cognitive impairments or to be medically unwell in the acute phase (74, 169, 236). Training and educational resources can improve application of assessments for clinical studies(153) however we first have to know which tools are commonly employed. At present there are no specific hospital protocols in place for cognitive and mood assessment post-stroke despite strategies for rehabilitation assessment and the route of care stroke patients should go through.(237, 238) Thus I sought to describe the cognitive/mood assessments used in contemporary published stroke trials in

study one and usual clinical practice across Scottish stroke care settings in study two.

2.2. Study One: Cognitive and mood assessment in stroke research - focussed review of contemporary studies

There are many measures available to assess for various post-stroke deficits. Stroke affects a range of functions at various stages. Therefore choice of test most appropriate to a research study is likely to vary. For recommendations to be made it is useful to describe current practice. I chose to perform a literature review to gather information on which assessments in cognition and mood are used in research to guide my later work.

2.2.1. Methods

I used a sensitive, focussed bespoke literature search strategy. Following informal review of similar research pertaining to functional assessments(153), a cognitive screening diagnostic test accuracy review(239) and stroke neuropsychological recommendations(22), along with knowledge of journal publication themes, I chose to restrict analysis to 16 journals selected based on relevance to stroke; impact factor and proportion of clinical studies. The journals selected were: the British Medical Journal (BMJ Publishing Group), The Journal of the American Medical Association (American Medical Association), The Lancet (Elsevier), The New England Journal of Medicine (Massachusetts Medical Society), Age and Aging (Oxford Journals), Journal of the American Geriatrics Society (The American Geriatrics Society), Lancet Neurology (Elsevier), Neurology (American Academy of Neurology), Journal of Neurology, Neurosurgery and Psychiatry (BMJ Publishing Group), American Journal of Psychiatry (American Psychiatric Publishing), Archives of Clinical Neuropsychology (Oxford Journals), Journal of the International Neuropsychological Society (Cambridge Journals), International Journal of Geriatric

Psychiatry (International College of Geriatric Psychoneuropharmacology), Stroke (American Heart Association), Cerebrovascular Diseases (Karger) and the International Journal of Stroke (World Stroke Organisation).

Following external peer review advice, a further 6 journals were added to broaden the scope of the search. These were: Neurorehabilitation and Neural Repair (Sage Journals), American Journal of Geriatric Psychiatry (Elsevier), Brain (Oxford Journals), International Psychogeriatrics (Cambridge Journals), European Journal of Neurology (Blackwell Publishing), Neuropsychologia (Elsevier). Journals representing general medicine; geriatric medicine/rehabilitation; neurology; psychology; psychiatry and stroke were included. (Figure 2-1)

General Medical: British Medical Journal, Journal of the American Medical Association, Lancet, New England Journal of Medicine

Gerontology/Rehabilitation: Age and Ageing, Journal of the American Geriatric Society, Neurorehabilitation and Neural Repair

Neurology: European Journal of Neurology; Lancet Neurology, Neurology, Journal of Neurology, Neurosurgery and Psychiatry

Psychiatry: American Journal of Psychiatry, American Journal of Geriatric Psychiatry; International Psychogeriatrics; International Journal of Geriatric Psychiatry,

Psychology: Archives of Clinical Neuropsychology, Brain; Journal of International Neuropsychology, Neuropsychologica

Stroke: Stroke, Cerebrovascular Diseases, International Journal of Stroke

Total papers screened n=80988

Total papers describing stroke survivors n=8826		
Stroke papers with cognitive/mood measures n=485		
	Total stroke papers	Total with cognitive/mood measures
General Medicine	316	9
Gerontology/Rehabilitation	475	25
Neurology	838	111
Psychiatry	75	41
Psychology	129	62
Stroke	6993	237

Stroke survivor studies with cognitive assessment n=330 (82% of all papers with cognitive/mood assessments)	Stroke survivor studies with mood assessment n=246 (64% of all papers with cognitive/mood assessments)
Number differing tests used n=300	Number differing tests used n=67

Figure 2-1 Search Strategy for assessing cognitive/mood measures in contemporary stroke trials

**Total papers with a cognitive or mood assessment had overlap and were counted in the number of papers with a cognitive assessment as well as those with a mood measure.*

Journals were hand searched for relevant articles January 2000 to October 2011 inclusive, reviewing all content, including letters and short reports. Inclusion criteria were: original research in adult, human stroke survivors. From these studies, I extracted details on any cognitive or mood assessments employed (including inclusion/exclusion criteria; primary outcome and secondary outcome(s)). Selection was deliberately inclusive. Where additional methodology was described in on-line or paper supplement this was accessed. I did not contact authors of manuscripts. Where a dataset was used more than once, with the same outcomes, the primary paper only was considered.

I used inclusive definitions of cognitive measures (any aspect of cognitive function including language and visuospatial/constructional skills) and mood. Where a neuropsychological battery was employed I listed the individual test components. Quality of life or global measures were included if they included a specific cognitive or mood component. Carer assessments and proxy assessments were included if they related to mood/cognition. Fatigue scales were not included.

Two researchers (a clinician, Dr Jennifer Harrison and myself) independently hand searched journals and compared results. Resulting lists of cognitive and mood measures were checked for relevance by an independent clinician (Dr Terrence Quinn) and a clinical psychologist (Dr Niall Broomfield). Final decision on inclusion was by group discussion and consensus. As a further validity check, an independent, blinded researcher (Dr Patricia Fearon) hand searched a random selection of four journals and four years. This search did not reveal any new studies, suggesting validity of the original searches. I described outcomes as absolute numbers of assessments and proportions.

2.2.2. Results

Across 22 journals, the total number of papers was 80988, with 8,826 (11%) papers detailing stroke survivor original research. Of these 485 (5%) had employed cognitive or mood assessment scales: 246 papers employing cognition measurement

only, 51 mood assessment only and 188 using both. Where cognitive/mood assessments were used, the median number of tests was 2 (IQR 1-3, range 1-21). A cognitive/mood measure was used as primary outcome in 353 (72% of papers with cognitive/mood measure); secondary outcome in 56 (11%) and as inclusion/exclusion criteria in 59 (12%). Psychiatry journals were most likely to detail cognitive/mood outcomes in stroke survivors (n=41 studies), although absolute number of stroke studies was modest (n=75 studies).

Total number of different cognitive/mood assessments was 367. Of 67 mood assessment scales used in 246 papers, the most prevalent were the Hamilton Rating Scale for Depression (n=43 [9% of all papers with cognitive/mood assessment]) and short form-36 health survey (n=40 papers [8%]). Where authors used their own cognitive assessments or did not specify what measure was used, these were excluded from total scale calculations. (Table 2-1)

Of 300 cognitive assessment scales used in 330 papers, 15 (5%) were clinical diagnostic criteria tests (i.e. the DSM-IV); 86 (29%) were neuropsychological test batteries or assessed multiple cognitive domains the remainder assessed single domains. The most prevalent assessments were Folstein's mini-mental state examination (n=180 [37%]) and Wechsler Adult Intelligence Scale (n=84 [16%]).

Table 2-1 prevalent cognitive/mood assessment modalities in contemporary published stroke research

Test	Number of papers % of total papers with cognitive/mood assessment (n=485)
Cognitive Measures †	
Mini Mental State Examination	180 (37%)
Wechsler Adult Intelligence Scale*	84 (17%)
Wechsler Memory Scale*	44 (9%)
Informant Questionnaire on Cognitive Decline in the Elderly	32 (7%)
Trail Making Tests A and B	28 (6%)
Mood Measures	
Hamilton Rating Scale for Depression	43 (9%)
Short Form-36 Health Survey	40 (8%)
Hospital Anxiety & Depression Scale	29 (6%)
Beck Depression Inventory	27 (6%)
Geriatric Depression Scale	25 (5%)

† “Authors own”; unspecified scales excluded

*subscales of battery

Included: vocabulary, similarities, information, comprehension, arithmetic, digit span, letter-number sequencing, picture completion, block design, matrix reasoning, digit symbol-coding and symbol search in various combinations or individually.

2.3. Study Two: Questionnaire assessment of usual practice in mood and cognitive assessment in Scottish stroke units.

This study was designed to determine if cognitive and mood assessments are being used in usual practice and if they are, do the assessments implemented correspond to the lack of consensus we found in study one.

2.3.1. Methods

2.3.1.1. Piloting

Questionnaire design and piloting was based on published guidance: The Canadian Medical Association Journals guide for self administered surveys; The Journal of Internet Medical Research web survey checklist (CHERRIES) and The International Journal for Quality; The International Journal for Quality in Health Care Good practice in conduct and reporting of survey based research (240-242) and the first part of this study demonstrating which cognitive/mood assessments are used in stroke research. I developed the questionnaire to assess key themes: Do practitioners assess mood/cognition? When and how are these assessments performed? How do these assessments inform management? A particularly challenging scenario is assessment of patients with communication impairments and I added a specific question on this.

I performed pilot work in two sites (Glasgow Western Infirmary and Glasgow Royal Infirmary) using a two-stage method. A draft template was circulated to representatives from stroke medicine; nursing and clinical psychology and discussed with individuals (in a focus group setting and through written comments collated by the authors). Content was revised using an informal discussion process, combining opinions of various members of the stroke multidisciplinary team (professors, consultants, registrars, nurses, occupational therapists and physiotherapists). The revised questionnaire was distributed to a wider group and allowed free-text

comments on phrasing and formatting. Comments were collated and decisions on final content were made based on authors' consensus.

2.3.1.2. Distribution

My final questionnaire was a one-page (A4) paper document with categorical and qualitative responses (Appendix B). I hosted the questionnaire on an open-access website. Responses were anonymous but I requested respondents' discipline and principal work place.

Mixed methodologies of distribution were used to ensure comprehensive coverage. The target group was all staff involved in direct stroke patient management across acute, rehabilitation and outpatient care. I contacted all Scottish, Stroke Managed Clinical Network (MCN) co-coordinators (n=12) to distribute the questionnaire across their network. I emailed specialist groups (Scottish Stroke Nurses Forum, Scottish Stroke Neuropsychologists, British Geriatric Society (Scotland), British Association Stroke Physicians, Stroke Allied Health Professionals and Association of Chartered Physiotherapists Interested in Neurology) and distributed paper copies through the U.K Stroke Forum delegate pack. Reminder emails and letters were sent round MCN co-coordinators who did not respond after 1 month. I checked responses against a list of hospitals providing stroke care using Scottish stroke care audit data.(243)

2.3.2. Analysis

For the data, I described absolute and percentage values, comparing responses across groups using Chi-square analysis (SPSS statistics 19, IBM). Qualitative data were grouped into shared themes by hand coding the free text responses.

This study was assessed by the manager and scientific officer for the West of Scotland Research Ethics Committee; formal Research Ethics approvals were not required (Appendix A).

2.3.3. Results

I received 174 responses, this comprised 10/14 (71%) Scottish Health Boards. Respondents represented most mainland Scottish health boards (Figure 2-2); Absolute number of returns was highest from Greater Glasgow and Clyde Health Board (n=55, 32% of all respondents). Respondents comprised medical staff (61, 35%), occupational therapists (27, 16%), other health professionals (including those that did not specify a profession) (27, 16%), nurses (23, 13%), psychologists (13, 7%), physiotherapists (12, 7%) and speech therapists (11, 6%). Respondents more routinely assessed cognition (n=148, 85%) than mood (n=119, 72%, $p<0.001$). Proportions of respondents performing cognitive/mood assessment were collated (Tables 2-2 and 2-3). Respondents reporting routine assessment of cognition varied by health board, there was no geographical difference in number of respondents reporting cognitive assessment ($p=0.879$) but there was for mood assessment ($p<0.001$). Glasgow and Greater Clyde Health Board had the highest number of respondents assessing mood (n=36, 21%).

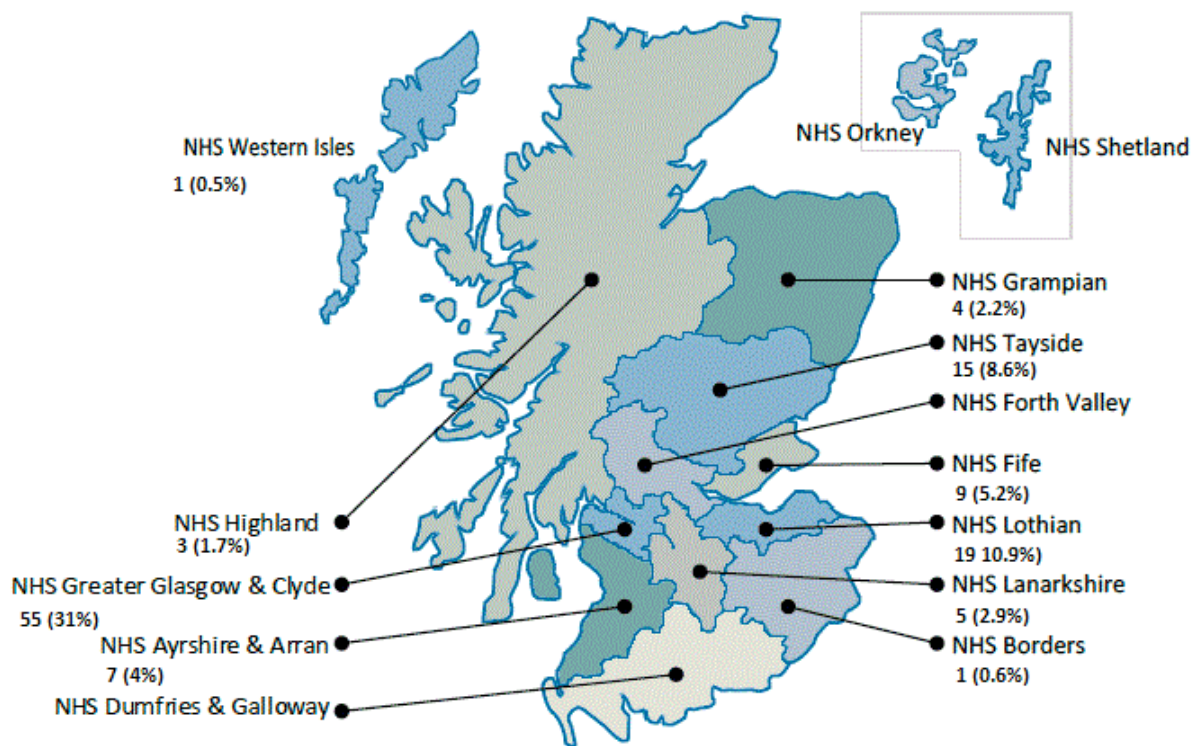


Figure 2-2 Survey response rates across Scottish NHS regions

**No responses were obtained from Dumfries and Galloway, Forth Valley, Orkney or Shetland NHS boards.*

A variety of tools were used for stroke survivor assessments (cognitive n=45 tools; mood n=17). The MMSE (158) (n=190, 32% of reported assessment use) and the HADS (197) (n=121, 53%) were the most commonly used. There was no difference in use of these measures across health boards (MMSE $p=0.078$, HADS $p=0.762$) or professions (MMSE $p=0.535$, HADS $p=0.953$) (Tables 2-2 to 2-6). Informal and bespoke methods were also prevalent, “observation” (n=22, 13%) and “informal questioning” (n=25, 14%).

I defined the ‘acute stroke’ setting as within the first 2 weeks of stroke; ‘rehabilitation’ was when patients had left the acute stroke ward and were receiving further care in a hospital or care facility (usually more than 2 weeks after stroke). Finally, outpatients were those that had been discharged from hospital facilities but could still be receiving treatment and support in the community or through clinic. We used percentages to describe frequency of responses due to the volume of responses given for each assessment across the settings: for example the MMSE may have been reported to be used across both the acute and rehabilitation setting by the same responder so all reports of usage were added up for each setting and then a % of the overall number of reports (in individual and all settings) was calculated.

Table 2-2 NHS board reports on using the MMSE and HADS across all settings

NHS Board	MMSE (n of reports all settings)	HADS (n of reports all settings)
Ayrshire and Arran	2	6
Boarders	1	1
Fife	5	6
Forth Valley	0	0
GG&C	40	23
Grampian	2	3
Highland	2	0
Lanarkshire	4	4
Lothian	13	11
Tayside	11	10
Western Isles	1	0

**Only one report required per member of that health board i.e. if MMSE was reported use in acute and rehabilitation setting by the reporter then it was only counted as 1 not 2.*

Table 2-3 Cognitive assessments performed by staff group

N (%) of each staff group performing cognitive assessment						
STAFF GROUP	TOTAL	MoCA	R-CAMCOG	AMT	ACE-R	MMSE
Nurses	22	4 (18%)	0	3 (14%)	2 (9%)	10 (45%)
Speech therapy	11	0	0	1 (9%)	1 (9%)	1 ((%)
Physiotherapy	12	0	0	2 (17%)	1 (8%)	0
OT	27	14 (52%)	0	4 (15%)	17/63%)	8 (30%)
Medical	61	10 (16%)	2 (3%)	42 (69%)	10 (16%)	38 (62%)
Psychology	13	3 (23%)	0	0	7 (54%)	3 (23%)
Other AHP	27	2 (7%)	0	5 (19%)	55 (19%)	6 (22%)

Table 2-4 Mood assessments performed by staff group

N (%) of each staff group performing mood assessment							
STAFF GROUP	TOTAL	HADS	PHQ-9	GHQ	DISCS	GDS	HRDS
Nurses	22	6 (27%)	4 (18%)	4 (18%)	2 (9%)	4 (18%)	0
SALT	11	0	1 (9%)	0	1 (9%)	0	0
Physiotherapy	12	0	0	0	0	0	0
OT	27	14 (52%)	1 (4%)	0	3 (11%)	1 (4%)	0
Medical	61	12 (20%)	0	0	2 (3%)	21 (34%)	1 (2%)
Psychology	13	9 (69%)	0	2 (15%)	3 (23%)	5 (38%)	0
Other AHP	27	5 (19%)	0	0	0	3 (11%)	1 (4%)

Table 2-5 Cognitive/mood assessment modalities used across various clinical settings

Test	Total (n) and %* of respondents reporting use of the test within each setting			
	All settings	Acute Stroke	Rehabilitation	Outpatient
Cognitive Assessments				
Folstein's Mini Mental State Examination	190 (32%)	71 (28%)	76 (30%)	43 (17%)
Hodkinson's Abbreviated Mental Test	125 (21%)	70 (28%)	32 (14%)	23 (22%)
Addenbrooke's Cognitive Examination	104 (18%)	24 (9%)	63 (27%)	17 (16%)
Montreal Cognitive Assessment	82 (14%)	25 (10%)	42 (18%)	15 (14%)
Cambridge Cognitive Examination	7 (1%)	2 (1%)	4 (2%)	1 (1%)
Mood Assessments				
Hospital Anxiety and Depression Scale	121 (53%)	30 (54%)	63 (53%)	26 (53%)
Geriatric Depression Scale	73 (32%)	21 (38%)	37 (30%)	15 (31%)
Depression Intensity Scale Circles	14 (6%)	2 (4%)	9 (7%)	3 (6%)
Patient Health Questionnaire	9 (4%)	1 (2%)	5 (4%)	3 (6%)
Hamilton Rating Scale for Depression	5 (2%)	0	5 (4%)	0

**percentages were based on the total number of ALL assessment responses made in each setting e.g. Cognitive assessments were reported to be used in all settings 589 times making 190 reports of MMSE 32% of total reports.*

**Table 2-6 Respondents reporting cognitive and mood assessment
described by professional group**

Professional Group (n total)	Routinely assess cognition n (%)	Routinely assess mood n (%)
Medical (61)	59 (96.7%)	49 (80.3%)
Occupational therapy (27)	26 (96.3%)	20 (74.1%)
Other health professionals* (27)	23 (85.2%)	17 (63%)
Nursing (23)	20 (87%)	17 (73.9%)
Psychology (13)	13 (100%)	12 (92.3%)
Physiotherapy (12)	5 (41.7%)	4 (33.3%)
Speech therapy (11)	6 (54.5%)	3 (27.3%)

**These were all other allied health professionals (dietitians and those who provided no response to staff group)*

From this sample, assessments were more commonly reported to be performed in hospital settings; cognitive assessment was mostly reported during first/acute admission (n=116, 67% of respondents, $p<0.001$) while mood was more commonly reported in rehabilitation settings (n=100, 58%, $p<0.001$). There was heterogeneity in reported management strategies for suspected cognitive/mood deficits (n=14 strategies described). For patients with possible cognitive/mood problems the most common reported management strategy was onward specialist referral (cognition n=62, 36%; mood n=71, 41%). If stroke survivors had a communication problem, the commonest reported approach was to seek advice from other specialties and have joint assessment and rehabilitation sessions (n=60, 34%). For mood, adapting the test to the patient (n=44, 25%) was the preferred approach in answers.

2.4. Discussion and conclusions

2.4.1. Study 1

Study one found that cognitive and mood assessments make up a very small percentage of published research. This could be because of poor reporting or lack of guidance surrounding choice of appropriate measure. Commonly used assessments are not universal across research. It is of course important to note, just because the reported percentage of published research dealing with cognition and mood assessment in stroke is relatively small, it cannot be concluded that no such work has been completed. Arguably, a further significant problem concerns the quality of work already produced. Many of the assessment tools used in existing research are heterogeneous, and further, there remains a lack of robust validation studies. Moreover, through not having a consensus of which cognitive and mood assessments to use in research, information declines and these problems and their effects remain poorly understood. In addition, as publications are not including cognitive and mood assessments as part of analysing stroke outcome, it is suggestive that stroke researchers do not put cognition and mood outcomes as a

priority in recovery despite knowing the negative effect these can have on rehabilitation.

Despite the clinical importance of cognitive and mood disorders, these aspects of stroke are infrequently measured in clinical research. When employed, cognitive/mood measures are most often used as the primary outcome, suggesting that researchers only measure these domains in studies focused on neuropsychology of stroke. My data suggest limited overlap between disciplines, psychology/psychiatry journals measure cognition and mood but infrequently study stroke cohorts, and the converse is true of neurology journals. Given the potential effect of cognitive/mood disorder on global functional outcome (145, 244), researchers are failing to measure what could be an important outcome (or indeed confounder) in stroke survivors. In not accounting for these issues, the results of the research (whether it is an experimental comparison or correlation) may be impacted, biasing the conclusions.

When cognitive/mood assessments are employed there is heterogeneity. It is also interesting to note that there were almost as many cognitive measures as there were studies describing cognitive function. This in part relates to my inclusive definition, comprising cognitive screening/assessment; single and multi-domain neuropsychological testing and dementia diagnostic criteria. Even limiting to single domain cognitive tests, the substantial heterogeneity in assessment strategies precludes meaningful between-study comparisons and meta-analyses.

Certain prevalent cognitive/mood assessments may not be appropriate for stroke cohorts, for example MMSE is not particularly suited to vascular cognitive impairment.(239) Conversely, certain scales prevalent in clinical practice were infrequently used in studies,(245) for example the MoCA (n=2 papers) and the Repeatable Battery for the Assessment of Neuropsychological Status (n=1 paper). Despite the variety of validated tools available, some authors continue to use their own bespoke assessment scales. As well as illustrating heterogeneity in assessments, the generated list of outcomes can be used to inform search strategies for future systematic reviews of diagnostic accuracy.

2.4.2. Study 2

Study two found that assessments commonly reported in research are not representative of those in usual practice. There is inconsistency as to what assessment is used and when (if at all). There was a general trend towards cognition measured earlier than mood. However, the cognitive and mood assessments chosen have not been validated properly in stroke cohorts. Lack of guidance as to how to test patients, stemming from inconsistent research, has continued this indecision into usual practice.

Study 2 demonstrates substantial heterogeneity in assessment and management of mood/cognition in stroke survivors. Use of 62 different assessment tools in a geographically small area clearly has implications for audit across services; research (shown in study 1) and service planning. Although the majority of respondents were assessing cognition and mood, not all were performing this routinely or across all settings. As with any questionnaire, presumably respondents in study 2 are more likely to have had an interest in cognition/mood and may not be representative of all healthcare professionals. I suspect that cognitive/mood assessment across all stroke services may be lower than suggested in this survey.

The use of non-validated, bespoke or informal assessments is a concern. Certain commonly used cognitive measures, although validated in other settings, may not be appropriate for stroke survivors. Folstein's MMSE does not perform consistently well in stroke (239, 246, 247) and ignores executive functioning, a common deficit in stroke populations; Hodkinson's Abbreviated Mental Test (AMT) has not been validated in stroke and the properties of ACE in stroke survivors is sensitive to timing of assessment (166, 169). For mood measures, there is a lack of research in the acute stroke setting (248) and we have no validated established norms for most tests in stroke populations (193, 239). The Hospital Anxiety and Depression Scale has been validated in stroke (201, 204, 249) but not the acute setting and the Geriatric Depression Scale has not been validated within stroke populations. International guidance documents for stroke cognitive and mood assessment are

available (22). The tools recommended in these texts (i.e. MoCA) were not commonly used in our sample. This is the foundation for the next chapters. I set out to describe the feasibility and the validity of these commonly used tools in the acute stroke setting.

As well as heterogeneity in assessment tools used, this work also demonstrates heterogeneity in application and intervention. The many different approaches reported for a commonly encountered, specific clinical scenario (the stroke survivor with aphasia) perhaps suggests the need for cognitive and mood assessment strategies specifically tailored to stroke survivors with language problems (250). With this in mind, assessments that have specifically been developed for those with language and visual problems (but not specifically for stroke survivors) will be included in the following works into feasibility and accuracy. Based on the responses and data we collected we were unable to draw clear conclusions on the practice of assessment within individual health boards/units. From the responses and data we collected, we would acknowledge as a limitation that we were unable to draw clear conclusions on the practice of assessment within individual health board/units. Due to the limited responses we collected, the popularity level of assessments could thus have been inflated, biasing the results. However, these data are still likely despite this limitation to provide some insight into assessments chosen by those who are interested in and find cognitive and mood assessments an important part of usual practice.

2.4.3. Strengths and limitations

Study one used a sensitive search strategy, employing hand searching and various validity checks. This approach has previously been successfully employed to describe functional outcomes in the stroke literature.(153) The increasing volume and multidisciplinary nature of stroke research precluded review across all studies.(251) However, my intention was to describe outcome assessments in popular medical journals rather than across the complete stroke literature. My

choice of journals was in keeping with other studies that have used similar methods.(252)

The strengths of our second study were the clear research questions and study design based on literature recommendations and robust piloting. The multi-modal questionnaire distribution will have ensured that most Scottish stroke staff had the opportunity to reply. The principle limitation was the modest response rate from certain regions. However, I achieved responses from most health boards and so I hope to have captured a reasonable snapshot of current practice, which may also give insight to usual practice in stroke units across the UK. I followed best practice in achieving maximal response rate (240, 253), but did not have the resource to offer financial incentives.

Despite this modest response, my survey gives the first National descriptions of usual practice within Scotland/UK.

Chapter 3 Test accuracy of direct patient cognitive screening tests for diagnosis of post-stroke cognitive impairment - systematic review and meta-analysis

Building on evidence presented in previous chapter

The previous chapter identified heterogeneity of assessment choice in stroke unit usual practice. The low percentage of stroke papers containing cognitive measures suggests that one of the reasons behind a lack of consensus is the lack of evidence demonstrating the accuracy and validity of certain measures administered to stroke cohorts. This chapter therefore investigates the accuracy of cognitive screening assessments to detect common post-stroke cognitive deficits (multi-domain cognitive impairment and all type dementia).

3.1. Introduction

A first step in management of cognitive problems is recognition and diagnosis. Informal clinician assessment will miss important cognitive problems (254) and formal cognitive assessment of stroke-survivors is recommended.(22, 150, 255) The ideal diagnostic strategy would be expert, multidisciplinary assessment, informed by comprehensive supplementary investigations. This approach is not feasible at a population level. In practice a two-step system is adopted, with baseline cognitive testing used for “screening” or “triage” and detailed specialist assessment available depending on the results.

Although there is general agreement on the merits of post-stroke cognitive assessment, there is no consensus on a preferred testing strategy.(22, 150, 255) Various cognitive screening tools are described with substantial variation in test strategies as demonstrated in the previous chapter.

The clinical “meaning” of cognitive problems after stroke will vary according to the context of testing. Cognitive impairment diagnosed in the first days post-stroke may reflect a mix of delirium, stroke specific impairments and pre-stroke cognitive decline.(25, 34, 53) In the longer term, cognitive assessment may be focussed on delineating cognitive strengths and/or weaknesses or on making or refuting a diagnosis of dementia. Common to all test situations is a final diagnosis of presence or absence of clinically (functionally) important, multi-domain impairments, based on expert assessment. A screening assessment should detect this syndrome of all-cause, post-stroke multi-domain cognitive impairment.

Collation and synthesis of the evidence describing test accuracy of available cognitive screening tools is an important first step to guide policy and practice and to highlight where there are knowledge gaps. I sought to perform systematic review and meta-analysis to describe the accuracy of screening tools for assessing dementia and multi-domain cognitive impairment in stroke-survivors.

3.2. Methods

I performed systematic literature review and meta-analysis using techniques developed for test accuracy reviews.(256) Where applicable I followed best practice in reporting. (257, 258) Study methods are described in further detail in the protocol. (Appendix C)

3.2.1. Aims

The co-primary aims were to describe:

- a) Test accuracy of cognitive screening tests for clinical diagnosis of multi-domain, cognitive impairment/dementia in stroke-survivors.
- b) Test accuracy of brief, cognitive screening tests against a more detailed neuropsychological assessment.

If data allowed, secondary objectives were to compare differing cut-point scores used to define a cut-off of “test positivity” and to compare the effects of heterogeneity with specific reference to test context and diagnostic reference standard.

3.2.2. Index test

Index tests of interest were any direct to patient, cognitive screening tests. I included any “screening” test where the authors described it as such. I excluded informant based assessments and tests that require testing equipment considered non-standard for a stroke service: brain-imaging modalities and various biomarkers (CSF, serum) that have been proposed as an aid to diagnosis of dementia. To date no single or combination of biomarkers is sufficiently sensitive or specific to make a diagnosis of dementia without corresponding clinical assessment and therefore is not standard in a stroke unit. I recognise that language and visuospatial function are important components of cognition, but did not include assessments of tools designed to exclusively test these domains. I did not include studies that compared one screening tool with no reference to a diagnostic gold standard.

For the second analysis, focus was “brief” screening tests, defined as any test that takes less than five minutes to complete.

3.2.3. Target condition and reference standard

The target condition of interest was all-cause multi-domain cognitive impairment post-stroke. This rubric recognises that a diagnosis of important post-stroke cognitive problems can be made without necessarily assigning a dementia label.

As reference standard, I included clinical diagnosis of dementia or dementia subtype made using any recognised classification system: the International Classification of Diseases 10th Edition, Mental and Behavioural Disorder (ICD-10, World Health Organisation), Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV, American Psychiatric Association) and for diagnostic criteria for specific subtypes of dementia described by NINDS-ADRDA for Alzheimer's type dementia and NINDS-AIREN for vascular dementia. I also included multi-domain, cognitive problems as detailed on a neuropsychological assessment provided the test battery was comprehensive (covering several cognitive domains in depth) and results were interpreted to give a diagnostic formulation. Single domain cognitive impairment or "cognitive impairment no dementia" were not included due to inconsistency in operationalisation of these syndromes.(259) In addition, I included both cross-sectional analyses for prevalent dementia and longitudinal follow-up for incident dementia, although these two study types will be analysed separately. I performed sub-analysis for studies conducted exclusively in acute stroke-unit; rehabilitation and community settings and subgroup analyses was pre-specified comparing dementia diagnosis and neuropsychological battery based diagnosis.

For assessment of brief tests, I accepted results from a more detailed multi-domain, screening assessment as reference standard, for example comparison of Hodkinson's AMT against Folstein's MMSE. The acceptable time frame between the index tests and the reference standard should either be on the same day or within 2 days if a cross sectional study or after 9 months if a delayed cross sectional /longitudinal study.

3.2.4. Participants and setting

My focus was stroke-survivors. Where study population was mixed, studies were included if the proportion of stroke-survivors was greater than 75%. I made no distinction between stroke subtypes but excluded studies of traumatic intracerebral haemorrhage and subarachnoid haemorrhage. I did not include case-studies (defined as having fewer than ten participants).

I included studies conducted in any clinical setting and at any time post-stroke. I operationalised time since stroke as “hyperacute” (first 7 days); “acute” (8-14 days); “post acute” (15 days-3 months); “medium term” (3-12 months) and “longer term” (post 1 year). I accepted a time delay of 6 to 9 months between index test and reference standard as acceptable due to the chronic nature of dementia and of multi domain cognitive impairment.(260, 261) As we were including papers of concurrent and predictive validity we felt this inclusion was reasonable especially considering the low numbers of papers in this research area.

All studies were included, but risk of bias associated with assessment timings was reported for individual papers using the “quality assessment” tool.

3.2.5. Search strategy

All aspects of searching, data extraction and study assessment were performed by two reviewers (myself and a neurologist, Dr Johann Selvarajah), based in separate centres and blinded to each-others’ results. On review of paired data, disagreement was resolved by discussion.

Dr Terence Quinn and I developed a sensitive search strategy in collaboration with an Information Scientist (Candida Fenton) and with assistance from the Cochrane Dementia and Cognitive Improvement Group.(Appendix D)

Search terms were developed using a concepts based approach employing Medical Subject Heading terms and other controlled vocabulary. Concepts of interest were “stroke”, “dementia” and “cognitive assessment”. Our “cognitive assessment”

concept included terms relating to cognitive tests used in stroke, based on previous survey data (Chapter 2). The sensitive search was supplemented with a purposive search, focussed on four prevalent cognitive screening tools: AMT, MMSE, MoCA and ACE-R.

I searched multiple, international, cross-disciplinary electronic databases from inception to January 2014. ALOIS (Cochrane Dementia and Cognitive Improvement Group); ARIF (University of Birmingham); CINAHL (EBSCOhost); Embase (OvidSP); LILACS (Bireme); Medline (OvidSP); MEDION (Netherlands); Psychinfo (OvidSP) and the DARE, NHS EED, HTA databases (CRD). I applied no language or date restrictions. I hand searched recent publications (2010 onwards) in key journals including conference proceedings (European Stroke Conference; International Stroke Conference; UK Stroke Forum; Age and Ageing; Cerebrovascular Diseases; International Journal of Stroke; Lancet Neurology; Stroke). Dr Quinn contacted groups with research interest in stroke test accuracy (Dr Ingrid Arevalo Rodrigue, author of Cochrane Collaboration review on MMSE; Dr Sarah Cullum, lead author of Cochrane Collaboration review on MoCA and Professor Nadina Lincoln, University of Nottingham, UK). I utilised “related article” feature in PubMed and examined key studies in the citation databases of Science Citation Index and Scopus. I also checked reference lists of relevant studies and reviews for further titles, repeating the process until no new titles were found.

I screened all titles generated by initial searches for relevance, corresponding abstracts were assessed and potentially eligible studies reviewed as full manuscripts against inclusion criteria by Dr Selvarajah and myself. As a check of internal validity, a random selection of 2,000 titles from the original search was reassessed by a third author (Dr Quinn). I tested external validity of our search by sharing lists of included papers with independent researchers (acknowledgements). One of my supervisors (Dr Quinn) identified exemplar papers relevant to the review question (Table 3-2) and he assessed whether these titles were detected by search strategy.

Table 3-1 Ten papers used for external validity check of search strategy

Paper Reference
Appels BA, Scherder E. The diagnostic accuracy of dementia-screening instruments with an administration time of 10 to 45 minutes for use in secondary care: A systematic review. <i>American Journal of Alzheimers Disease and other Dementias</i> 2010; 25(4):301-316.
Blake H, McKinney M, Treece K, Lee E, Lincoln NB. An evaluation of screening measures for cognitive impairment after stroke. <i>Age and ageing</i> .2002;31:451-456
Bour A, Rasquin S, Boreas A, Limburg M, Verhey F. How predictive is the MMSE for cognitive performance after stroke. <i>Journal of neurology</i> . 2010;257;630-7.
Crawford S, Whitnall L, Robertson J, Evans JJ. A systematic review of the accuracy and clinical utility of the Addenbrooke's Cognitive Examination and the Addenbrooke's Cognitive Examination-Revised in the diagnosis of dementia. <i>Int J Geriatr Psychiatry</i> 2011.
Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. <i>Journal of Neurology, Neurosurgery and Psychiatry</i> 2007;78:790-9.
de Koning I, van Kooten F, Dippel DWJ, van Harskamp F, Grobbee DE, Kluft C, Koudstaal PJ. The CAMCOG: a useful screening instrument for dementia in stroke patients. <i>Stroke</i> .1998;29:2080-2086.
Kwa VIH, Limburg M, Voogel Aj, Teunisse S, Derix MMA, Hijdra A. Feasibility of cognitive screening in patients with ischaemic stroke using the CAMCOG. A Hospital Based Study. <i>Journal of Neurology</i> .1996;243:405-409.
Nokleby K, Boland E, bergersen H, Schanke AK, Famer L, Wagle J, Wyller TB. Screening for cognitive deficits after stroke; a comparison of three screening tools. <i>Clinical rehabilitation</i> .2008; 22:1095-1104.
Srikanth V, Thrift AG, Fryer JL, Saling MM, Dewey HM, Sturm JW, Donnan GA. The validity of brief screening cognitive instruments in the diagnosis of cognitive impairment and dementia after first-ever stroke. <i>International Psychogeriatrics</i> .2006;18:295-305.
Young J, Meagher D, MacLulich A. Cognitive assessment of older people. <i>British Medical Journal</i> . 2011;343: d5042 doi: 10.1136/bmj.d5042

3.2.6. Data extraction and management

I extracted data to a study-specific, pro-forma, piloted against two papers.(166, 239)

For screening tests that give an ordinal summary score, various cut-points can be used to define “test positive” cases. Where data were given for a number of cut-offs, I extracted separate data for each. Where a study may have included useable data but these were not presented in the published manuscript I contacted the authors directly via email. If the same data set was presented in more than one publication, only the primary paper was included.

3.2.7. Quality assessment

Myself and Dr Selvarajah independently assessed quality of study reporting using the dementia specific extension to the Standards for Reporting of Diagnostic Accuracy (STARDdem) checklist.(Appendix E) I assessed methodological quality using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2).(262) Dr Quinn and I had previously developed QUADAS-2 “anchoring statements” specific to cognitive assessment.(260) The process of statement development is illustrated in Figure 3-1 and Appendix F.

Papers gathered on diagnostic accuracy studies of dementia.

A group of 10 various health care professionals with experience in cognitive impairment went through Quadas-2 statements and discussed phrasing relevant to dementia using two pilot papers.

Statements were modified and rephrased to fit with review question and format of papers.

Selection of 10 papers were split up between groups of two and scored using discussed statements.

Problems that arose with statement phrasing were discussed and modified to fit the general review question.

Figure 3-1 Flow chart of developing anchoring statements for QUADAS 2

3.2.8. Statistical analysis

I assessed accuracy of screening tests against a dichotomous variable cognitive impairment/no cognitive impairment. I created standard “two-by-two” data tables, describing binary test results cross-classified with binary reference standard. I did not include case-control studies in pooled analyses. I used accepted cut-offs for multi-domain impairment/dementia published in the literature: ACE<88; R-CAMCOG <33; MMSE<27 and <25. For MoCA, a cut-off of <26 was used together with the lower cut-off of <22 since the former was developed to detect single rather than multi-domain impairment.

Where data allowed I calculated sensitivity, specificity and corresponding 95% confidence intervals (95% CI) and created test accuracy forest plots (RevMan 5.1, Cochrane Collaboration). I pooled test accuracy data using the bivariate approach (Statistical Analysis Software v9.1, SAS Institute Inc, USA). This assumes that the pooled random effects model takes into account the heterogeneity between studies and assessments. The bivariate approach in meta-analysis pools together (the usually negatively correlated) all sensitivity and all specificity from various studies, analysing them separately. From this a Receiver Operating Characteristic (ROC) curve can determine a single summary measure of accuracy for each pair of sensitivity and specificity. This summary point is also known as the Diagnostic Odds Ratio (DOR): the odds of a positive index assessment result in subjects with the disease divided by the odds of a positive result in someone without the disease. This accounts for both between study variation and within study variation such as the criteria used to define ‘disease positive’ and the heterogeneity of symptoms/signs in the examined cohort.(220, 263) Dr Quinn and I used a bespoke macro developed with assistance of a statistical team with an interest in test accuracy.(264) Summary metrics of interest were sensitivity/specificity and positive/negative likelihood ratios.(265) Dr Quinn created summary curves in ROC space with corresponding 95% prediction intervals.

I assessed potential heterogeneity through visual inspection of forest plots. I pre-specified two factors that may contribute to heterogeneity, timing of assessment

and reference standard. We (myself and Dr Quinn) dichotomized studies into “acute” (classified as hyperacute or acute) or “non-acute” and described reference standard as “clinical” (clinical diagnosis of dementia) and “neuropsychological battery” (multi-domain cognitive impairment). Where sufficient studies were available, I assessed effect by plotting summary ROC curves by covariate and calculating relative sensitivity and specificity. Here, relative sensitivity and specificity refers to the meta-analysis of sensitivity and specificity across all settings. These values are calculated by taking all studies (handling acute and non acute studies separately) and calculating an overall measure for sensitivity and specificity in each setting. The acute values were then divided by their non-acute partners (e.g. acute sensitivity/non acute sensitivity). From general statistical principles that apply to likelihood ratios and risk ratios, a 95% confidence interval was calculated. Thus, if the ratio was >1 then sensitivity or specificity was greater in the acute setting and whereas if <1 sensitivity or specificity was larger in non-acute settings.

I did not quantify publication bias, as there is no assessment applicable to test accuracy.

Where papers fulfilled inclusion criteria but did not have data suitable for this method of analysis I offer a tabulated/narrative description.

3.3. Results

From 19,182 titles, I reviewed 241 full papers of which 35 papers (34 datasets) (164-166, 169, 187, 236, 239, 246, 247, 266-292) were suitable for inclusion. Scope of included literature was international, with papers from 16 differing countries.

I detailed the study selection process in a PRISMA flow diagram.(Figure 3-1)

The validation check suggested the initial search was appropriate, as all pre-specified papers were found on first search.



Figure 3-2 PRISMA flow diagram detailing review process

3.3.1. Accuracy of screening tools for diagnosis of cognitive impairment

From the papers identified in the original search using MESH terms, we screened 511 abstracts and excluded 270 due to irrelevance to our chosen themes of diagnostic test accuracy and dementia.

In total n=35 papers (n=3562 participants) were eligible. (164-166, 169, 187, 236, 239, 246, 247, 266-289) I tabulated summary descriptors for studies employing clinical diagnosis reference standard (n=11 papers) (187, 236, 267, 275, 277-279, 284, 286-288) and those using detailed neuropsychological assessment (n=21). (164-166, 169, 239, 246, 247, 266, 268-274, 276, 280-283, 285)(Tables 3-3 and 3-4)

There was considerable heterogeneity in study population; setting and test strategy. Twenty-three differing tests were described, commonest MMSE (n=16 papers) and MoCA (n=8).(Tables 3-3 to 3-5).

The various screening tests gave a spread of test accuracy, sensitivity range: 14-100% and specificity range: 0-100% with “trade-off” between sensitivity and specificity. Where authors compared more than one test in the same population, the comparator was usually MMSE and for most papers MMSE was more specific and less sensitive than other tests. Both the Executive Function Performance Test (EFPT) and the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) showed strong correlations with scores on neuropsychological batteries but data were not suitable for pooled analysis.(266, 268, 270, 273)

The recruitment strategy, demographics of stroke population included and the country in which this study was completed are detailed in table 3-6.

Table 3-2 Test accuracy for individual studies: Limited to those studies where reference standard was a clinical diagnosis of dementia

Study	“n” included	“n”(%) with dementia	Index test (cut-off	Summary Results	
				Sensitivity	Specificity
Brookes* (275)	152	N/A	BMET	Discriminates AD/SVD	
Cumming 2010 (267)	149	42 (28%)	Cog4	53%	84%
De Koning 2000 (277)	300	55 (19%)	RCAMCOG (<33)	91%	90%
De Koning 2005 (278)	121	35 (29%)	RCAMCOG (<33)	66%	94%
De Koning (288)	300	55 (19%)	CAMCOG (<81) MMSE (<25)	91% 80%	80% 67%
Dong 2012 (279)	300	60 (25%)	MoCA (<21) MMSE (<24)	88% 88%	64% 67%
Hershey(282)	63	13 (21%)	CCCE (<20)	85%	87%
Hobson* (236)	149	69 (46%)	PNB (<55)	71%	93%
Srikanth (187)	67	8 (12%)	MMSE (<23)	14%	100%
Tang (284)	142	10 (12%)	MDRS (<22) MMSE (<18)	82% 80%	90% 88%
Wu (286)	206	95 (46%)	MoCA (<23)	65%	79%

Where more than one test cut-off was described, we present the authors primary data.

N/A=not applicable

ASU=Acute Stroke Unit

NPB=Neuropsychological battery

BMET= Brief Memory and Executive Test; CSCSE=Cognitive Capacity Screening Examination; Cognistat=Neurobehavioral Cognitive Status Examination; Cog4=Cognitive components of the National Institutes of Health Stroke Scale; MMSE=Mini-mental State Examination; MoCA=Montreal Cognitive Assessment; PNB=Preliminary Neuropsychological Battery; CAMCOG= Cambridge Cognitive Examination; R-CAMCOG=Rotterdam Cambridge Cognitive Examination; MDRS=Mattis Dementia Rating Scale

*=case-control study, data not included in any pooled analyses

Table 3-3 test accuracy data for individual studies: Limited to those studies where reference standard was diagnosis of cognitive impairment based on detailed, multi-domain neuropsychological battery

Study	“n” included	“n” (%) with dementia	Index test (cut-off)	Summary Results	
				Sensitivity	Specificity
Agrell* (246)	64	N/A	MMSE (<23)	56%	24%
Baum* (266)	73	N/A	EPFT	Correlates with NPB	
Blake (239)	112	31 (28%)	MMSE (<24)	62%	88%
Bour (271)	194	22 (11%)	MMSE (<23)	96%	83%
Cartoni (276)	30	27 (90%)	MEAMS (≥3)	52%	100%
Cumming 2013 (164)	60	39 (65%)	MMSE (<24)	54%	81%
			MoCA (<24)	97%	52%
Desmond* (272)	72	6 (8%)	TICS (25)	100%	83%
			MMSE (<24)	83%	87%
Dong 2010 (280)	100	60 (60%)	MMSE (<24)	86%	82%
			MoCA (<21)	90%	77%
Godefroy (165)	95	64 (67%)	MMSE (<24)	70%	94%
			MoCA (<24)	92%	58%
Grace (281)	70	32 (46%)	MMS (<79)	69%	79%
			MMSE (<24)	44%	84%
Green (268)	60	N/A	RBANS (<84)	84%	90%
Jodzio (283)	44	25 (55%)	WCST	PPV 21	NPV 75
Larson (273)	158	N/A	RBANS	Correlates with NPB	
Morris (169)	101	51 (84%)	MMSE (<24)	58%	77%
			ACE-R (<88)	94%	0%
Nokleby (287)	49	28 (60%)	COGNISTAT (<59)	59%	67%
			SINS (>2)	71%	67%
			CDT(9)	63%	67%
Nys* (247)	72	N/A	MMSE (<28)	100%	40%
Pendlebury (166)	91	19 (21%)	MoCA (<25)	100%	46%
			MMSE (<24)	56%	96%
			ACE-R (<88)	84%	85%
Pendlebury (telephone) (274)	91	19 (21%)	T-MoCA (<19)	89%	46%
			TICSm (<25)	85%	56%
Salvadori (269)	80	47 (59%)	MoCA (<21)	91%	76%
Wolf (270)	20	N/A	EPFT	Correlates with NPB	
Wong* (285)	68	N/A	MoCA (<21)	73%	75%

Where more than one test cut-off was described, we present the authors primary data.

N/A=not applicable

ASU=Acute Stroke Unit

NPB=Neuropsychological battery

CDT=Clock drawing test; CSCSE=Cognitive Capacity Screening Examination;

Cognistat=Neurobehavioral Cognitive Status Examination; Cog4=Cognitive components of the

National Institutes of Health Stroke Scale; EPFT=Executive Performance Function Test;

MEAMS=Middlesex Elderly Assessment Mental State; MMSE=Mini-mental State Examination;

MMS=Mini-Mental State; MoCA=Montreal Cognitive Assessment; T-MoCA: Telephone Montreal

Cognitive Assessment; PNB=Preliminary Neuropsychological Battery; RBANS=Repeatable Battery for

Assessment of Neuropsychological Status; SINS=Screening Instrument Neuropsychological

impairments in Stroke; TICS=Telephone Interview Cognitive Status; TICSm=Modified Telephone

Interview Cognitive Status; WCST= Wisconsin Card Sorting Test

**=case-control study, data not included in any pooled analyses*

Table 3-4 Summary of included studies: Limited to "acute" settings

Study	Setting	Time since stroke	Includes aphasia	Index test(s)	Index test rater	Diagnostic test(s)	Diagnostic test rater
Bour 2010 (271)	Neurology ward	Acute	no	MMSE	Psychologist	NPB	Psychologist
Cumming 2013 (164)	Not Specified	Acute	Not specified	MMSE, MoCA	Not specified	NPB	Not specified
Dong 2012 (279)	ASU	Hyperacute	no	MoCA, MMSE	Not specified	NPB	Psychologist
Dong 2010 (280)	ASU	Hyperacute	no	MoCA, MMSE	Not specified	Clinical	Not specified
Godefroy 2011 (165)	ASU	Acute	Yes	MoCA, MMSE	Not Specified	NPB	Not specified
Green 2013 (268)	ASU	Acute	Not specified	RBANS	Researcher	NPB	Researcher
Jodzio 2010 (283)	Neurology ward	Acute	No	WCST	Not specified	NPB	Not specified
Morris 2012 (169)	ASU	Acute	Yes (mild)	ACE-R, MMSE	Physician, Psychologist	NPB	Psychologist
Nys 2005 (247)	ASU	Acute	Yes	MMSE	Not specified	NPB	Not specified
Salvadori 2013 (269)	ASU	Hyperacute*	Yes (mild)	MoCA	Researcher	NPB	Not specified
Wu 2013 (286)	ASU	Not specified	No	MoCA	Physician	Clinical	Not specified

Where more than one test cut-off was described, we present the authors primary data.

N/A=not applicable

ASU=Acute Stroke Unit

NPB=Neuropsychological battery

ACE-R=Addenbrooke's Cognitive Examination Revised; MMSE=Mini-mental State Examination; MoCA=Montreal Cognitive Assessment; NPB=Neuropsychological Battery; RBANS=Repeatable Battery for Assessment of Neuropsychological Status.

**=case-control study, data not included in any pooled analyses*

Table 3-5 Summary of included studies: Limited to "non acute" settings

Study	Setting	Time since Stroke	Include Aphasia	Index test(s)	Index test rater	Diagnostic test(s)	Diagnostic test rater
Agrell 2000 (246)	Rehabilitation	Post acute	No	MMSE	Physician	NPB	Psychologist
Baum 2008 (266)	Community	Post acute	Not specified	EFPT	Not specified	NPB	Not Specified
Blake 2002 (239)	Hospital (other)	Not specified	Not specified	MMSE SST RCPM	Not specified	NPB	Not Specified
Brookes 2012 (275)	Rehabilitation	Post acute	Not specified	BMET MMSE CDRS	Not specified	Clinical	Not Specified
Cartoni 2005 (276)	Rehabilitation	Not specified	No	MEAMS	OT	NPB	Psychologist
Cumming 2010 (267)	Community	Long term	Yes	MMSE Cog4	Physician Psychiatrist	Clinical	Physician Psychiatrist
de Koning 2000 (277)	Neurology Ward	Medium term	No	(R)- CAMCOG	Physician Psychologist	Clinical	Adjudication Panel
de Koning 2005 (278)	Hospital (other)	Medium term	No	R- CAMCOG	Researcher	Clinical	Adjudication Panel
de Koning 1998 (288)	Outpatients	Post acute	Yes (mild)	CAMCOG MMSE	Not specified	Clinical	Adjudication Panel
Desmond 1994 (272)	Outpatients	Not specified	Not specified	TICS	Not specified	NPB	Not Specified
Grace 1995 (281)	Rehabilitation	Not specified	No	MMSE 3MS	Not specified	NPB	Not Specified
Hershey	Outpatients	Not	No	CCSE	Mixed	Clinical	Physician

1987 (282)		specified		FAQ			
Larson 2005(273)	Rehabilitation	Medium term	Yes (mild)	RBANS	Not Specified	NPB	Not Specified
Nokleby 2008 (287)	Rehabilitation	Post acute	Yes	Cognistat SINS CDT	Physician Psychologist	NPB	Psychologist
Pendlebury 2012 (166)	Outpatients	Long term	No	MMSE MoCA ACE-R	Physician	NPB	Mixed
Srikanth 2006 (187)	Outpatients	Post acute	Yes	S-MMSE	Not Specified	Clinical	Not Specified
Tang 2005 (284)	Outpatients	Post acute	Not specified	MDRS MMSE	Researcher	Clinical	Psychiatrist
Wolf 2010 (270)	Rehabilitation	Hyper- acute	Yes	EFPT	Not Specified	NPB	Not Specified
Wong 2009 (285)	Rehabilitation	Post acute	Not specified	MoCA	Researcher	NPB	Researcher

N/A=not applicable

MCI=Mild Cognitive Impairment; NPB=Neuropsychological battery; ASU=Acute Stroke Unit

BMET= Brief Memory and Executive Test; CDRS=Clinical Dementia rating Scale; CCSE=Cognitive Capacity Screening Examination; Cognistat=Neurobehavioural Cognitive Status Examination; Cog4=Cognitive components of the National Institutes of Health Stroke Scale; EPFT=Executive Performance Function Test; MEAMS=Middlesex Elderly Assessment Mental State; MDRS=Mattis Dementia Rating Scale; MMSE=Mini-mental State Examination; MMS=Mini-Mental State; 3MS:Modified Mini-Mental State; S-MMSE=Standardised Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; RBANS=Repeatable Battery for Assessment of Neuropsychological Status; RCPM=Raven's Coloured Progressive Matrices; CAMCOG=Cambridge Cognitive Examination; R-CAMCOG=Rotterdam Cambridge Cognitive Examination; SST=Stop Signal Task; SINS=Screening Instrument Neuropsychological impairments in Stroke; TICS=Telephone Interview Cognitive Status; TICSm=Modified Telephone Interview Cognitive Status; WCST= Wisconsin Card Sorting Test

Table 3-6 Study demographic details

Study	Country	Recruitment method	Time since stroke (weeks)	Aphasics included	Mean Age (years)
Agrell 2000 (246)	Sweden	Consecutive	2 to 8	No	77
Baum 2008 (266)	USA	Selected	24	Unspecified	64.5
Blake 2002 (239)	UK	Research population	Unspecified	Unspecified	70.8
Bour 2010 (271)	Netherlands	Consecutive	4	No	68.3
Brookes 2012 (275)	UK	Case control	>12	Unspecified	69.7
Cartoni 2005 (276)	UK	Consecutive	Unspecified	No	75.8
Cumming 2010 (267)	Australia	Unspecified	12	Unspecified	80.3
Cumming 2013 (164)	Australia	Research population	72	Yes	72.1
de Koning 2000 (277)	Netherlands	Research population	12 to 36	No	69.2
de Koning 2005 (278)	Netherlands	Research population	12 to 36	No	70

de Koning 1998 (288)	Netherlands	Consecutive	12 to 36	Yes	69.2
Desmond 1994 (272)	USA	Research population	Unspecified	Unspecified	72.3
Dong 2010 (280)	Singapore	Unspecified	<2	No	61.2
Dong 2012 (279)	Singapore	Consecutive	<2	No	60.2
Godefroy 2011 (165)	France	Consecutive	<3	Yes	68.2
Grace 1995 (281)	USA	Consecutive	Unspecified	No	Unspecifie d
Green 2013 (268)	UK	Consecutive	Unspecified	Yes	67.7
Hershey 1987 (282)	USA	Research population	Unspecified	No	66.2
Hobson 2003 (236)	UK	Consecutive	Unspecified	Unspecified	72.8
Jodzio 2010 (283)	Poland	Convenience	<4	No	56
Johnson- Greene 2009	USA	Convenience	<2	no	70.4
Larson 2005(273)	USA	Consecutive	≤24	Yes	63.7
Lees 2013	UK	Consecutive	<1	Yes	74

Morris 2012 (169)	UK	Consecutive	2	Yes	76
Nokleby 2008 (287)	Norway	Selected	9.5	Yes	62
Nys 2005 (247)	Netherlands	Consecutive	<1	yes	64.7
Pendlebury 2012 (166)	UK	Research populations consecutive	>52	No	72
Salvadori 2013 (269)	Italy	Unspecified	Unspecified	Unspecified	68.2
Srikanth 2006 (187)	Australia	Research population	4 and 52	Yes	69
Tang 2005 (284)	Hong Kong	Consecutive	12	Unspecified	71
Wolf 2010 (270)	USA	Research population	1	yes	58.8
Wong 2009 (285)	Hong Kong	Random selection	Unspecified	Unspecified	70
Wong 2004	Hong Kong	Prospective selection	12	Unspecified	72.9
Wu 2013 (286)	China	Consecutive	unspecified	Unspecified	68.14

Meta-analysis

I was able to pool test accuracy data for four tests: ACE-R (cut-off score <88); MMSE (cut-offs ≤ 24 and ≤ 26), MoCA (cut-offs <26 and <22) and R-CAMCOG (cut-off <33). No test had sensitivity and specificity that were significantly different from others. MoCA at “traditional” cut-off was sensitive at cost of specificity; specificity improved if cut-offs were adjusted. (Table 3-8, Figures 3-4 to 3-11)

Table 3-7 Pooled test accuracy for four cognitive screening tests against a reference standard of "cognitive impairment"

Test (threshold)	Papers Patients	Cognitive impairment n (%)	Sensitivity (95%CI)	Specificity (95%CI)	Positive Likelihood Ratio (95%CI)	Negative Likelihood Ratio (95%CI)
ACE-R (<88/100)	2 (192)	52 (27%)	96.2 (0.90-1.0)	0.70 (0.59-0.80)	3.19 (2.24-4.54)	0.06 (0.01-0.22)
MMSE (<25/30)	12 (1639)	483 (30%)	0.71 (0.60-0.80)	0.85 (0.80-0.89)	4.73 (3.63-6.17)	0.34 (0.25-0.47)
MMSE (<27/30)	5 (445)	195 (44%)	0.88 (0.82-0.92)	0.62 (0.50-0.73)	2.33 (1.72-3.17)	0.19 (0.13-0.29)
MoCA (<22/30)	6 (726)	289 (39%)	0.84 (0.76-0.89)	0.78 (0.69-0.84)	3.75 (2.77-5.08)	0.20 (0.15-0.29)
MoCA (<26/30)	4 (326)	131 (40%)	0.95 (0.89-0.98)	0.45 (0.34-0.57)	1.73 (1.43-2.10)	0.10 (0.04-0.23)
R-CAMCOG (<33/49)	2 (421)	90 (21%)	0.81 (0.57-0.93)	0.92 (0.87-0.95)	10.18 (6.41-16.18)	0.20 (0.07-0.52)

ACE-R=Addenbrookes Cognitive Examination (Revised); MMSE=Folstein's Mini Mental state Examination; MoCA=Montreal Cognitive Assessment; R-CAMCOG=Rotterdam CAMCOG

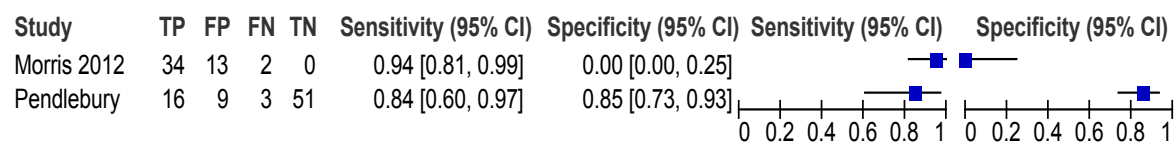


Figure 3-3 Forest plot of ACE-R (cut-off 88) for diagnosis of dementia/cognitive impairment (n=2 studies)

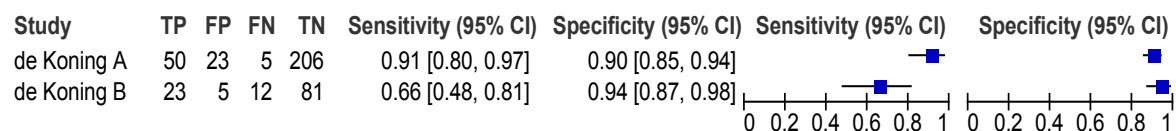
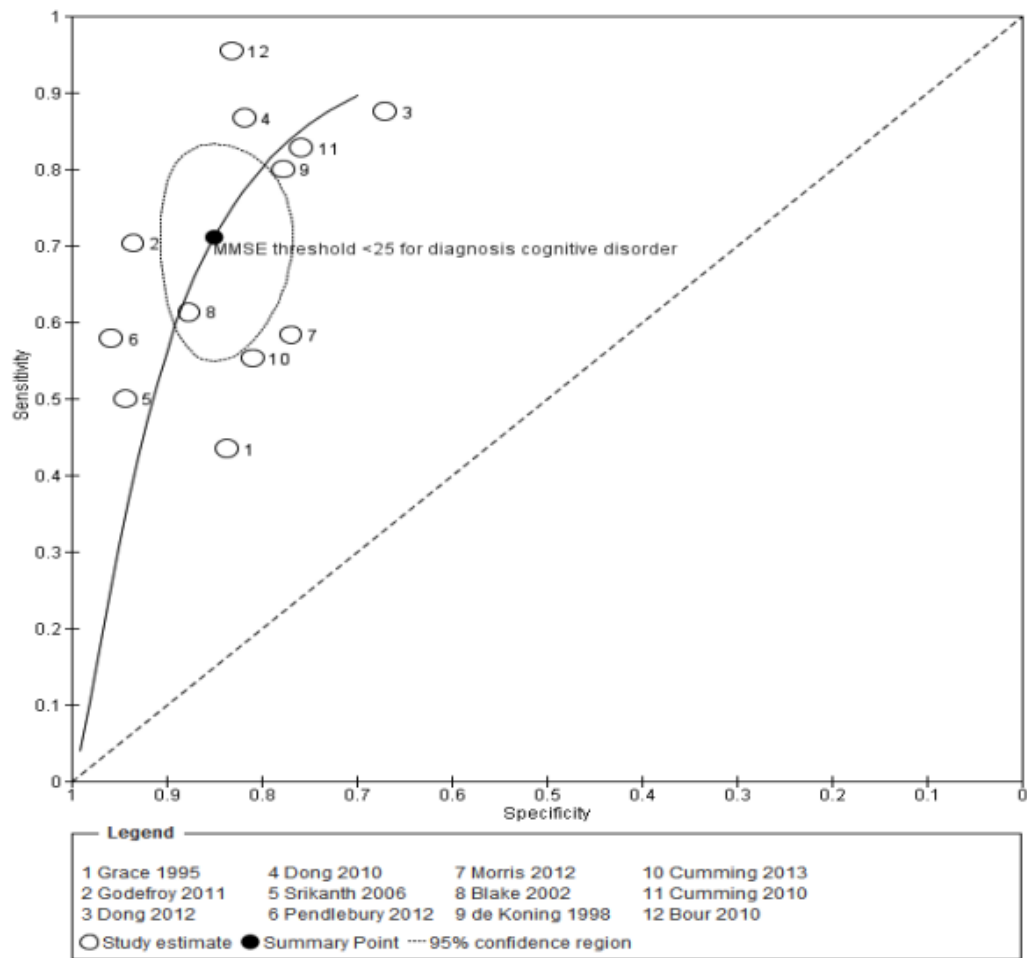
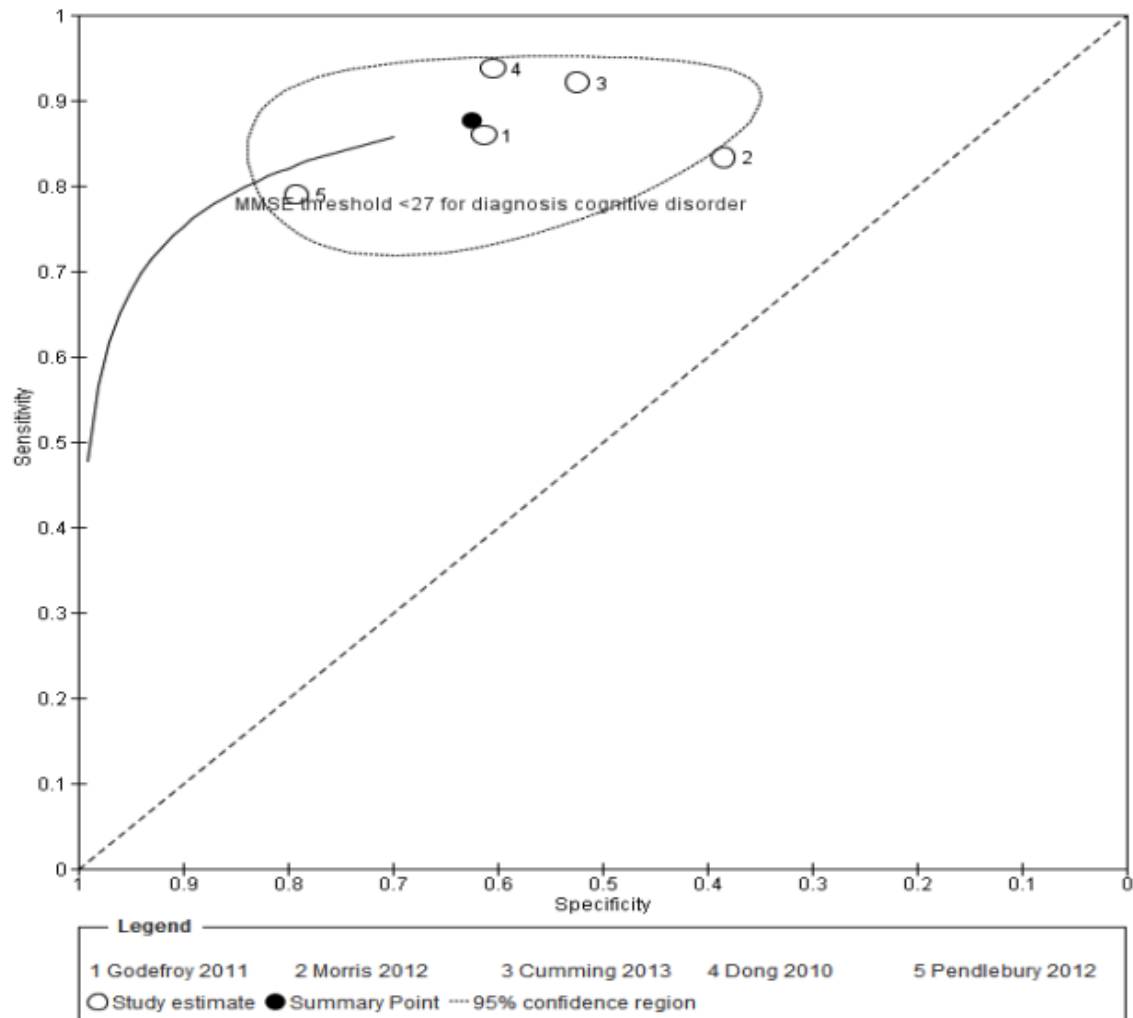


Figure 3-4 Forest plot of R-CAMCOG (cut-off 33) for dementia/cognitive impairment (n=2 studies)



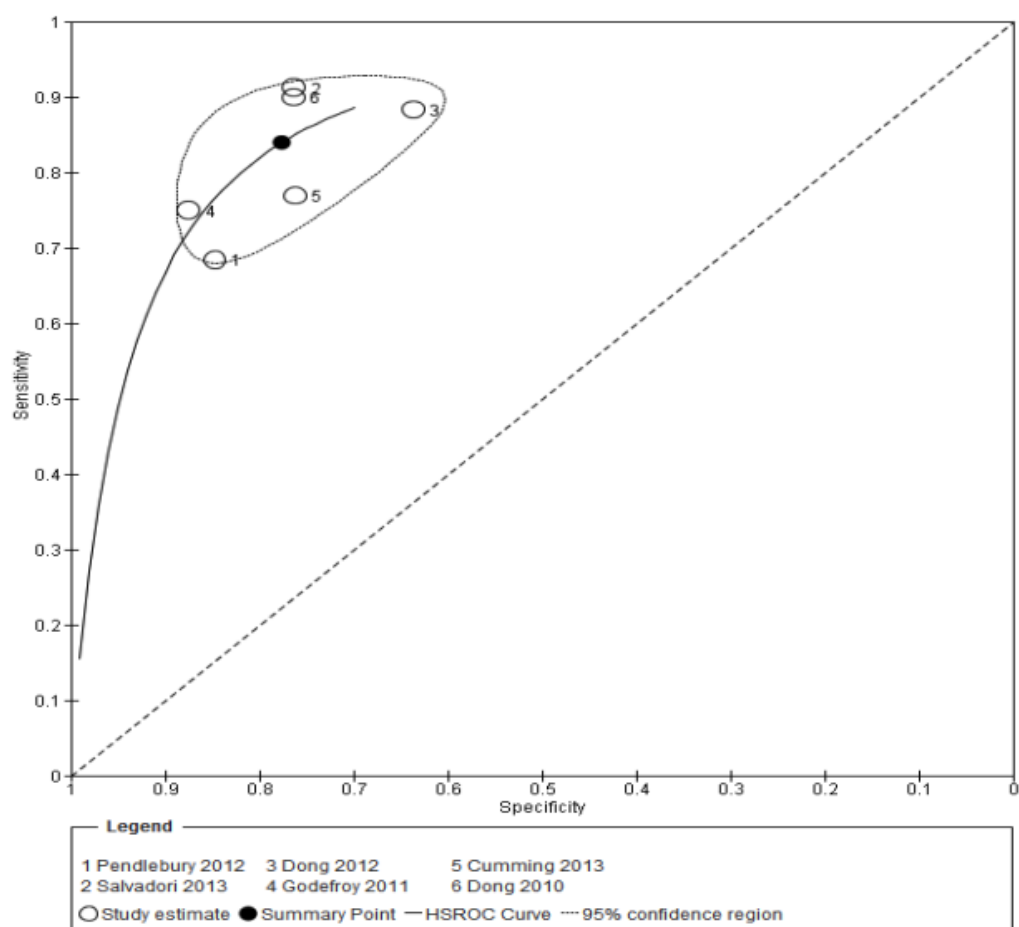
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blake 2002	19	10	12	71	0.61 [0.42, 0.78]	0.88 [0.78, 0.94]		
Bour 2010	21	29	1	143	0.95 [0.77, 1.00]	0.83 [0.77, 0.88]		
Cumming 2010	48	22	10	69	0.83 [0.71, 0.91]	0.76 [0.66, 0.84]		
Cumming 2013	21	4	17	17	0.55 [0.38, 0.71]	0.81 [0.58, 0.95]		
de Koning 1998	44	51	11	178	0.80 [0.67, 0.90]	0.78 [0.72, 0.83]		
Dong 2010	52	10	8	45	0.87 [0.75, 0.94]	0.82 [0.69, 0.91]		
Dong 2012	28	32	4	65	0.88 [0.71, 0.96]	0.67 [0.57, 0.76]		
Godefroy 2011	45	2	19	29	0.70 [0.58, 0.81]	0.94 [0.79, 0.99]		
Grace 1995	20	9	26	46	0.43 [0.29, 0.59]	0.84 [0.71, 0.92]		
Morris 2012	21	3	15	10	0.58 [0.41, 0.74]	0.77 [0.46, 0.95]		
Pendlebury 2012	11	3	8	69	0.58 [0.33, 0.80]	0.96 [0.88, 0.99]		
Srikanth 2006	4	4	4	67	0.50 [0.16, 0.84]	0.94 [0.86, 0.98]		

Figure 3-5 Summary ROC curve and forest plot describing test accuracy studies of Folstein's Mini-Mental State Examination (MMSE) at a test cut-off of <25/30



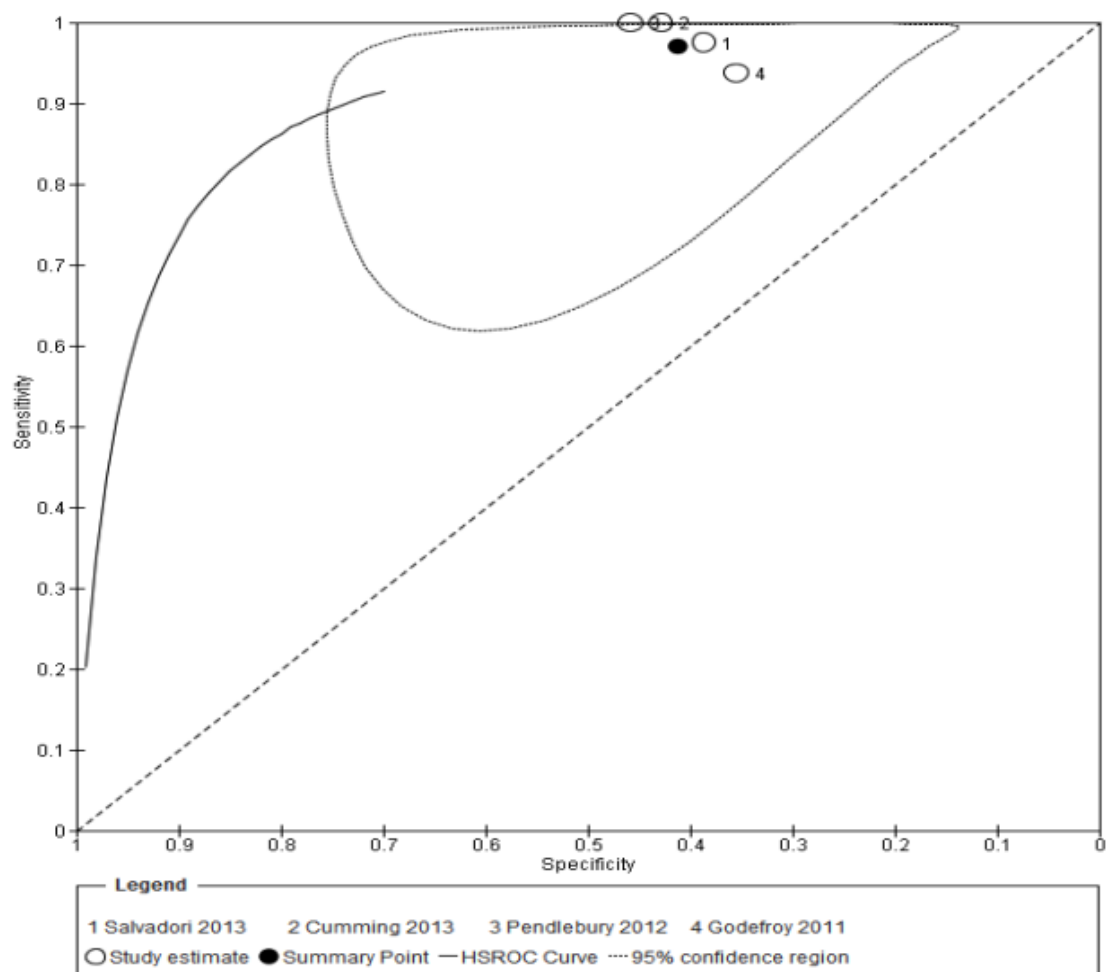
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cumming 2013	35	10	3	11	0.92 [0.79, 0.98]	0.52 [0.30, 0.74]		
Dong 2010	45	17	3	26	0.94 [0.83, 0.99]	0.60 [0.44, 0.75]		
Godefroy 2011	55	12	9	19	0.86 [0.75, 0.93]	0.61 [0.42, 0.78]		
Morris 2012	30	8	6	5	0.83 [0.67, 0.94]	0.38 [0.14, 0.68]		
Pendlebury 2012	15	15	4	57	0.79 [0.54, 0.94]	0.79 [0.68, 0.88]		

Figure 3-6 Summary ROC curve and forest plot describing test accuracy studies of Folstein's Mini-Mental State Examination (MMSE) at a test cut-off of <27/30



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cumming 2013	30	5	9	16	0.77 [0.61, 0.89]	0.76 [0.53, 0.92]		
Dong 2010	54	13	6	42	0.90 [0.79, 0.96]	0.76 [0.63, 0.87]		
Dong 2012	53	65	7	114	0.88 [0.77, 0.95]	0.64 [0.56, 0.71]		
Godefroy 2011	48	4	16	28	0.75 [0.63, 0.85]	0.88 [0.71, 0.96]		
Pendlebury 2012	13	11	6	61	0.68 [0.43, 0.87]	0.85 [0.74, 0.92]		
Salvadori 2013	73	18	7	58	0.91 [0.83, 0.96]	0.76 [0.65, 0.85]		

Figure 3-7 Summary ROC curve and forest plot describing test accuracy studies of the Montreal Cognitive Assessment (MoCA) at a test cut-off of <22/30



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cumming 2013	39	12	0	9	1.00 [0.91, 1.00]	0.43 [0.22, 0.66]	■	■
Godefroy 2011	60	20	4	11	0.94 [0.85, 0.98]	0.35 [0.19, 0.55]	■	■
Pendlebury 2012	19	39	0	33	1.00 [0.82, 1.00]	0.46 [0.34, 0.58]	■	■
Salvatori 2013	78	46	2	29	0.97 [0.91, 1.00]	0.39 [0.28, 0.51]	■	■

Figure 3-8 Summary ROC curve and forest plot describing test accuracy studies of the Montreal Cognitive Assessment (MoCA) at a test cut-off of <26/30

3.3.2. Quality and reporting

One paper was graded “low risk” for all QUADAS2 domains.(269) Common issues of concern were use of case-control methodology (n=7 papers) and potential lack of blinding (n=12).(Figure 3-2 and 3-3). Five papers attempted to include patients with moderate to severe aphasia.(165, 187, 269, 270)

STARDdem assessment suggested consistent areas of poor reporting, particularly around the handling of missing data (n=22 papers) and descriptions of training and expertise of assessors (n=25 papers).(Table 3-8)

Due to the modest sample size of the papers relevant to this research question, post-hoc analysis based on study quality or sample size was not performed. I chose to describe quality at an individual paper level using standardised measures (QUADAS2 and STARDdem).

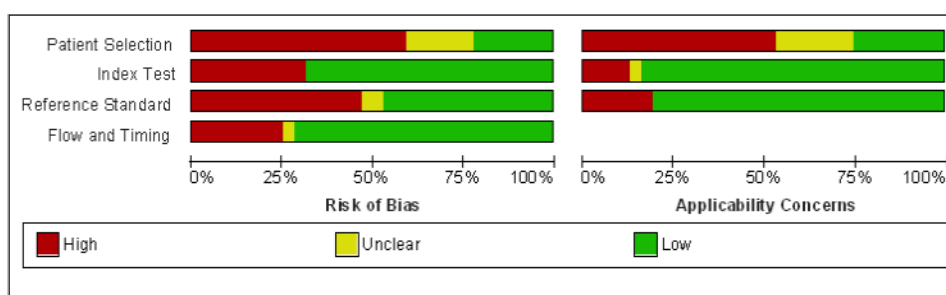


Figure 3-9 Assessment of risk bias and applicability concerns using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2)

Table 3-8 Risk of bias and applicability concerns assessed at study level using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2)

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Agrell 2000	+	+	+	+	+	+	+
Baum 2008	+	+	?	+	+	+	+
Blake 2002	?	+	?	+	?	+	+
Bour 2010	?	+	+	+	?	+	+
Brookes 2012	+	+	+	+	+	+	+
Cartoni 2007	?	+	+	+	?	+	+
Cumming 2010	+	+	+	+	+	+	+
Cumming 2013	?	+	+	+	?	+	+
de Koning 1998	+	+	+	+	+	+	+
de Koning 2000	+	+	+	+	+	+	+
de Koning 2005	+	+	+	+	+	+	+
Desmond 1994	+	+	+	+	+	+	+
Dong 2010	?	+	+	+	?	+	+
Dong 2012	+	+	+	+	+	+	+
Godefroy 2011	+	+	+	+	+	+	+
Grace 1995	+	+	+	+	+	+	+
Green 2013	+	+	+	+	?	+	+
Hershey 1987	+	+	+	+	+	+	+
Hobson 2003	+	+	+	+	+	+	+
Jodzio 2010	+	+	+	+	+	?	+
Larson 2005	+	+	+	+	+	+	+
Morris 2012	+	+	+	+	+	+	+
Nokleby 2008	+	+	+	?	+	+	+
Nys 2005	+	+	+	+	+	+	+
Pendlebury 2012	+	+	+	+	+	+	+
Salvadori 2013	+	+	+	+	+	+	+
Sodring 1998	+	+	+	+	+	+	+
Srikanth 2006	+	+	+	+	+	+	+
Tang 2005	?	+	+	+	?	+	+
Wolf 2010	+	+	+	+	+	+	+
Wong 2009	+	+	+	+	+	+	+
Wu 2013	+	+	+	+	+	+	+

High
 Unclear
 Low

Methods														Results																	
Participants														Test Methods				Stats		Participants				Test Results				Estimates			
STARDdem item																															
STUDY AUTHOR	1	2	25	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24						
Agrell 2000	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N						
Baum 2008	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	N	N	N	N	Y	Y						
Blake 2002	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	Y	N	N	Y	N	Y	N						
Bour 2010	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N						
Brookes 2012	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	N	N	Y	Y						
Cartoni 2007	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N						
Cumming 2010	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N						
Cumming 2013	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y						
de Koning 2000	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N						
de Koning 2005	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N						
de Koning 1998	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N						
Desmond 1994	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y						
Dong 2012	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N						
Dong 2010	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	Y	Y	N	N	Y	Y	Y	N						
Godefroy 2011	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	N	Y	N	Y	N						
Grace 1995	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	Y	Y	N	N	Y	N	Y	N						
Green 2013	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	Y	N						
Hershey 1987	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	N	Y	N	Y	N						
Hobson 2003	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y						
Jodzio 2010	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N						
Larson 2005	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	N						
Morris 2012	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	N						
Nkleby 2008	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	N						
Nys 2005	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	Y	Y	N	N	Y	N	N	N						
Pendlebury 2012	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N						
Salvadori 2013	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N						
Srikanth 2006	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N						
Tang 2005	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	N	Y						
Wolf 2010	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	N	N	N	Y	N	N	N						
Wong 2009	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	N	N	Y	N	N	Y						
Wu 2013	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N						
Pendlebury 2013	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N						

Figure 3-10 STARDdem reporting guidance as applied to included studies

3.3.3. Heterogeneity

I assessed effect of timing and reference standard using MMSE data. Comparing six “acute” studies(236, 246, 265, 269, 277, 278) and six “non-acute”; (166, 247, 267, 274, 275, 279) relative sensitivity:0.73 (95%CI:0.58-0.93) and relative specificity:1.12 (95%CI:1.01-1.25) suggesting that accuracy varies with assessment timing. (Figure 3-10) Comparing “clinical dementia” reference standard, (187, 269, 280, 284, 288) against neuropsychological battery; (164, 166, 169, 239, 279, 281, 293) suggested no difference with relative sensitivity:0.86 (95%CI:0.67-1.11) and relative specificity:1.05 (95%CI:0.95-1.16). (Figure 3-11)

3.3.4. Accuracy of brief tools

I found three suitable papers (n=294 participants). (289, 290, 292) (Table 3-9) The 4AT test is a brief delirium assessment. However, it was included here as a brief assessment of cognition as delirium can be a trigger to the development of longer-term cognitive impairment, as discussed previously in the introduction chapter (p5). Two papers were graded high risk of bias and applicability concerns due to case control-methodology and patient inclusion. (289, 292)

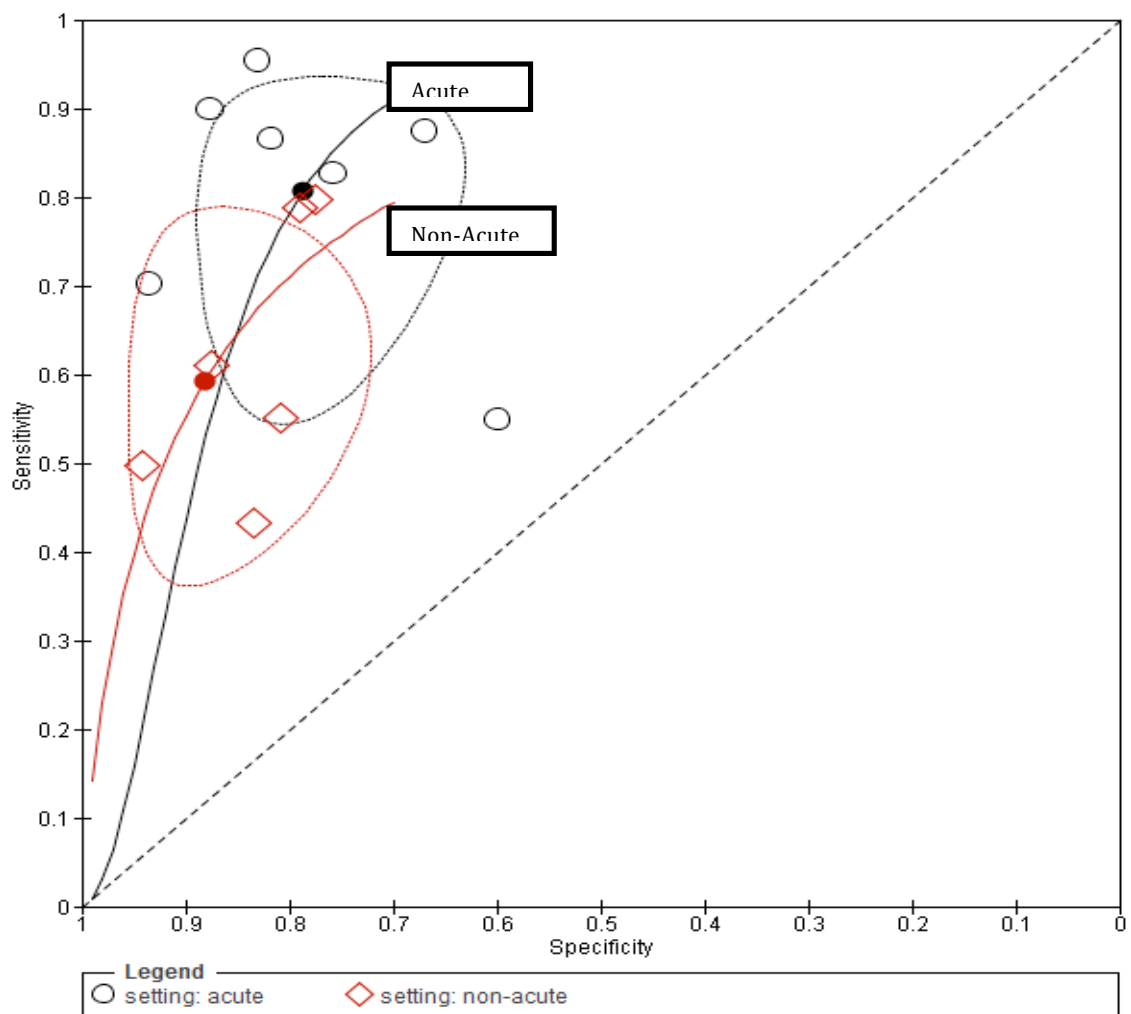


Figure 3-11 Summary ROC curve exploring the effect of time since stroke on test accuracy: comparing "acute" testing with "non-acute" testing

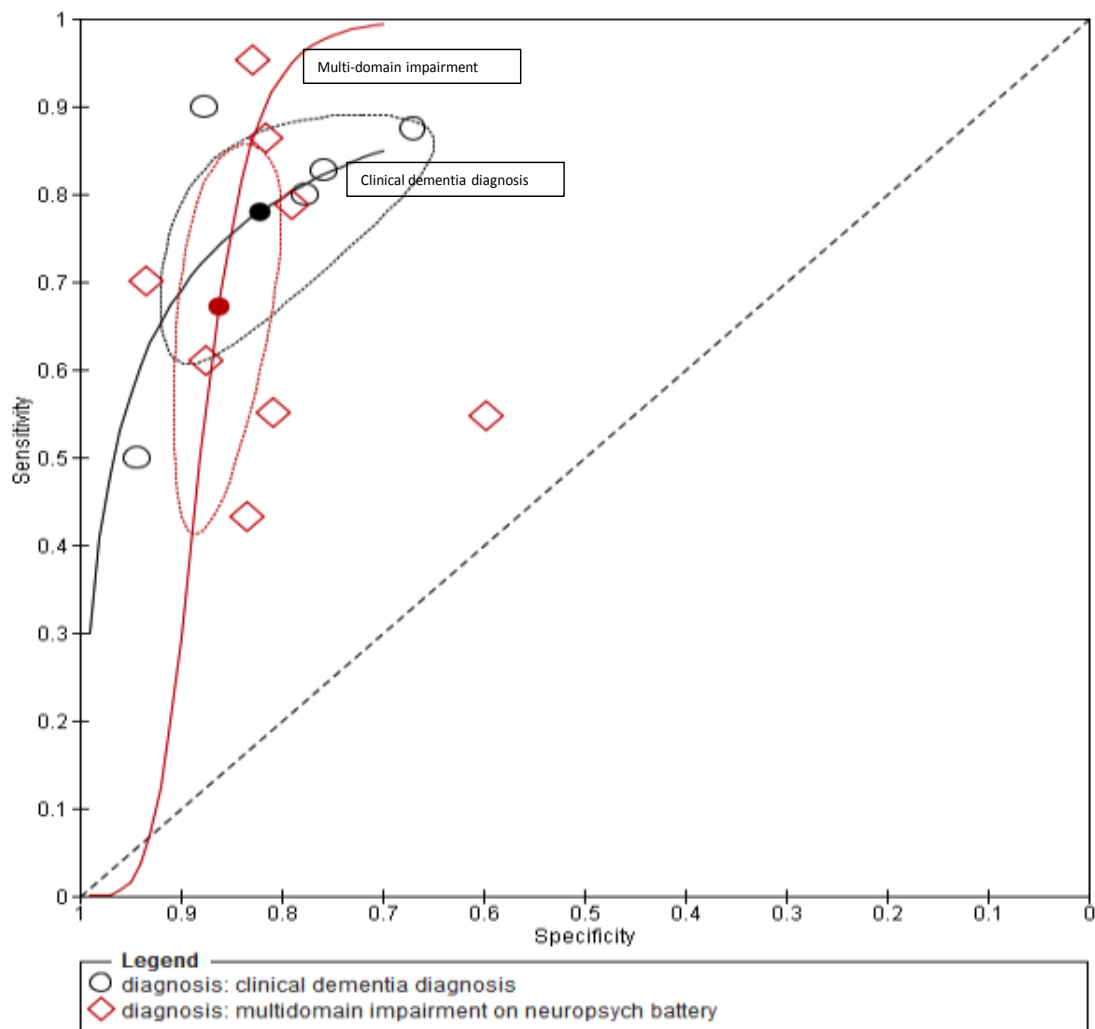


Figure 3-12 Summary ROC curve exploring the effect of reference standard employed: comparing "clinical" diagnosis of dementia against diagnosis made using "neuropsychological battery"

Table 3-9 Summary of studies describing brief (less than 5 minutes administration time) cognitive assessments

Study	"n" Included	Setting (Timing)	Index Tests	Reference Standard(s)	Summary results
Johnson-Greene 2009	115	ASU (Hyperacute)	TCT	MMSE, HVLT	TCT correlates with HVLT and MMSE and discriminates cases from controls
Lees 2013	111	ASU (Hyperacute)	4AT, AMT, CDT, Cog-4	MoCA	4AT performs well at standard MoCA cut-offs. CDT performs well at lower MoCA cut-offs
Wong 2004	68	Outpatients (Unspecified)	CDT	MMSE, WCST	CDT correlated with MMSE and WCST and discriminates cases from controls

ASU=Acute Stroke unit

4AT=4 A test; AMT=Abbreviated mental test; Cog-4=Cognitive components of the National Institute of Health Stroke Scale; CDT=Clock drawing test; TCT=Three Cities Test

HVLT=Harvard Verbal Learning Test; MMSE=Mini Mental State Examination; MoCA=Montreal Cognitive Assessment; WCST=Wisconsin Card Sorting Test

3.4. Discussion

The aim was to provide a synthesis of screening tool properties to allow evidence-based recommendations on cognitive testing. I was partially successful in this aim. Although there is an extensive literature describing cognitive testing in stroke, number of papers using the classical test accuracy paradigm of index test versus reference (gold) standard was limited. Eligible papers were characterised by heterogeneity and risk of bias and the potential to describe summary analyses at individual test level was limited.

Accepting these caveats, I can still offer conclusions from the pooled analysis. There was no clearly superior cognitive screening test. Given the relative consistency in accuracy data across the tests, choice of test strategy should be informed by purpose of testing and other factors such as feasibility; acceptability and opportunity cost. Recent guidance and practice has tended to favour novel tests over the traditionally popular MMSE.(22, 255, 291) Although there may be good reasons to favour other tests, the data I present do not suggest that MMSE is inferior for the diagnosis of multi-domain impairment, albeit MMSE may lack sensitivity for single domain impairment.(166, 259, 291) There was a trend towards better clinical utility for R-CAMCOG but the small number of studies and corresponding wide confidence intervals precludes definitive recommendation.

Preferred test properties will depend on the assessment setting and on test purpose, particularly the level of cognitive impairment to be detected. High sensitivity may be desired but this will be at the expense of lower specificity: false positives will rise. These patients may have to undergo further testing and may over burden services preventing true positives from receiving help. On the other hand, favouring specificity will raises the false negative rate, and some patients will miss out on support and treatments, perhaps impacting negatively on patient recovery. Therefore, it may be argued that for initial screening, sensitivity should be preferred over specificity. In this case MoCA may be preferred. The high false positive rate for multi-domain impairment obtained at a cut-off of MoCA<26 is to be expected since this cut-off was chosen for detection of single domain

impairment/MCI.(166, 259) This study findings suggest that an adjusted cut-off of <22 has improved properties for multi-domain impairment.

I was pragmatic in choice of index test and reference standard. The screening test rubric ranged from relatively short assessments (MoCA) through to fairly lengthy batteries (RBANS). I did not find significant improvements in sensitivity/specificity comparing shorter and longer screens (e.g. MoCA and ACE-R). This may suggest that increasing the length of screening tools does not necessarily improve the test accuracy.

There is no universally accepted gold standard for dementia. Clinical diagnosis is most in keeping with current practice, but I acknowledge the inherent inter-observer variability.(260) Including multi-domain impairment based on neuropsychological assessment is potentially problematic. A-priori Dr Quinn and I decided on this approach, to maximise potential for pooled analysis and recognising that a clinical diagnosis is not always feasible or appropriate. I used multi-domain impairment as this is closest to current operational classifications of dementia; I did not specify the contents of the neuropsychological assessment and recognise substantial heterogeneity in batteries employed.(259) It is reassuring that subgroup analyses suggested no significant difference between the approaches to reference standard.

Brief assessment tools are attractive for use in busy stroke settings but only if they have acceptable accuracy. In this regard the limited number of studies looking at brief assessments is unfortunate. Based on data available, screening using clock drawing test or AMT may have a role for initial assessment; but with their focus on select cognitive domains they should not be considered a substitute for subsequent multi-domain testing. However, The 4AT assessment is a brief delirium assessment. However it may have potential for brief cognitive assessment. It embodies items pertaining to orientation, memory (both long and short term) and attention, which can be commonly affected following stroke. Thus, the 4AT assessment could provide credible information of the patients' current and future cognitive ability, hence its inclusion here.(290, 294) However, the 4AT is an extremely brief

assessment and therefore not likely to give an accurate global assessment of cognition (i.e. covering areas of executive function, abstract reasoning or visual spatial ability which are all affected by stroke and impact on cognition long term).

3.4.1. Limitations of included studies

This review highlights issues in the design and reporting of cognitive test accuracy studies. There was little reporting of missing or indeterminate data, however we know that substantial numbers of stroke patients are unable to complete multi-domain screening tools. The same concern holds for a reference standard based on an extensive neuropsychological battery. Limiting test accuracy data to those able to complete testing will bias results, tending to inflate test accuracy. I would encourage use of the “intention to diagnose” approach, where the traditional “2x2” test accuracy table is expanded with cells representing those unable to complete index test and/or reference standard.(295)

A related issue is around generalisability of the included subjects. In the quality assessment we (Dr Selvarajah and I) scored several papers as “inappropriate exclusion” including the studies that excluded patients with moderate to severe aphasia or inability to consent. I recognise the challenges of cognitive testing in this group, who by definition have at least single domain impairment, however excluding patients with communication problems or frank confusion from test accuracy research will limit external validity.

I would encourage greater consistency in reporting of methods and results. Use of the recently published STARDdem guidance may improve reporting.(Table 3-2)

3.4.2. Strengths and limitations of review

I offer a comprehensive review with highly sensitive search strategy; following best practice in conduct and reporting and with multiple embedded internal and external validity checks. The review has limitations, the focussed question excluded

potentially informative papers, for example where screening tests are compared against each other,(163, 296) and I did not assess other important test metrics such as responsiveness to change. I recognise that cognitive assessment in stroke is evolving, 15 (47%) of included papers in the primary review were published since 2010. Novel, stroke specific(297) and generic cognitive screening tools (ACE version three) have been described but no accuracy data were available at the time of review. We are limited in our analyses by the modest number of papers describing only a limited range of available tests. We used those cut-offs described in the papers. Access to source data and pooling in an individual patient level meta-analysis would allow for a more robust assessment of how varying thresholds may perform.

3.4.3. Future research

The subgroup analysis suggests that test accuracy will vary depending on time since stroke but could not suggest an optimal time for assessment. Early assessment in the ASU has practical advantages and could allow for timely intervention. However few studies assessed patients in the very acute period. Given the issues with generalisability and missing data, future studies may wish to describe feasibility and acceptability of testing as well as classical test accuracy metrics.

3.4.4. Conclusion

As studies have focussed on using one assessment versus a reference standard, a meta-analysis comparing the same assessments across similar populations provides the best way to analyse assessment performance within stroke cohorts. There is no clearly superior cognitive screening test approach. If sensitivity is favoured, then MoCA may be the preferable test, although test cut-offs may need adapted for use in stroke. All of our results must be interpreted with caution as included studies had substantial heterogeneity and potential for bias. I would also acknowledge that multi-domain cognitive impairment is part of, but is not the same as, a diagnosis of

dementia. A diagnosis of dementia requires evidence of both impairment in activities of daily living, progression and a lack of reversibility. Importantly, none of these are measured by the cognitive screening tools described in this work and thus there are inherent limitations in using any form of cognitive screening to predict future dementia. I recognise that our reference standard contains two approaches that are not synonymous. The true gold standard is clinical assessment. To make a diagnosis of dementia using usual classification systems requires evidence of a) impairment in functional ability, b) progression, c) lack of reversibility and d) impairments in more than one cognitive domain. Multi-domain cognitive assessment (and screening tools) only assesses the last of these four criteria.

3.4.5. Research in context

There is an extensive, cross-disciplinary literature on cognitive screening in stroke. Previous systematic reviews of cognitive test accuracy have focussed on older adults with narrative results only. My review provides a contemporary synthesis of the rapidly evolving field of cognitive screening in stroke and uses novel statistical techniques to allow summary analyses. My pooled data suggest that no cognitive test is clearly superior, R-CAMCOG has potential and MoCA has favourable sensitivity. Sub-analyses suggest that timing of assessment will impact on test properties and that screening test diagnostic cut-offs should be altered for stroke-survivors and where purpose of testing is to detect dementia versus single domain impairments.

Although in practice the results of cognitive screening would be interpreted as part of a multidisciplinary assessment that includes other functional and investigational data, it can help put results in context to model the effect of test property data. From the annual incidence of all strokes (152,000) in the UK(298), Glasgow has an annual stroke survival of 2,257.(299) Assuming a one-year prevalence of all-cause post-stroke dementia of around 40%, at traditional cut-offs MoCA as sole screening

tool would miss 45 patients with dementia and would wrongly give a probable dementia diagnosis to 745 patients. If the MoCA cut-off is adjusted to $<22/30$, multi domain cognitive impairment/dementia could be missed in 144 patients and 298 would be given an erroneous dementia label. However, the outcome of any assessment is vulnerable to other external factors i.e. assessor experience and setting administered. This is further discussed in chapter 7.

Chapter 4 Feasibility and diagnostic accuracy of early mood screening to diagnose persisting clinical depression or anxiety disorder post-stroke

Building on evidence presented in previous chapters

My systematic review suggested that cognitive screening assessments at the acute stage post-stroke is feasible but with limited data on accuracy and where data were available accuracy differed between tools.

There is less research into standardised assessment of post-stroke mood than cognition. Like cognition, mood can significantly impact on a patient's outcome across several areas of recovery. This work follows the previous chapter and explores the feasibility and predictive accuracy of mood measures administered to acute stroke patients.

4.1. Introduction

Post-stroke depression usually starts within the first year, with around a third developing within 3 months. With that said half of those that develop depression within the first year also recover. Despite this the impact on recovery within this time may still impact beyond the first year.(87) It is therefore important to screen for potential depression early as it would allow for timely support, education and treatment to reduce risk of hindering recovery.

In addition, early assessment for neuropsychological disorders is a pertinent issue as many stroke survivors are discharged direct from the acute ward and if

depression/anxiety is not assessed during this stay it may not be assessed thereafter. Stroke-survivors often report that their physical needs are prioritised over psychological.(300)

Depressed stroke survivors are more passive in their approach to rehabilitation and show reduced functional ability on admission and discharge.(146) Mood impacts on both their ability to perform activities of daily living(143) and on their rate of functional recovery during rehabilitation.(202) Effects persist during follow up: depressed patients show a decrease in some areas of functional ability.(149) Association does not imply causation. There is a clear link between mood and function but research to date can only tell us that one increases the risk and predicts the severity of the other.(145, 301, 302)

Mood assessment in the first few days after stroke may be complicated by impairments of speech; cognitive and physical function. Communication deficits can lead to depression post-stroke(96), but also can limit the assessment measures that are feasible and may predispose to inaccurate diagnosis(214, 215) However, stroke patients may also demonstrate changes in mood due to the realisation of a potentially catastrophic life event. Psychological adjustment to stroke often involves depression and/or anxiety symptoms, which do not persist long-term and significantly affect recovery.(303, 304) By using predictive accuracy, it might be possible to find an assessment that can identify those individuals who fail to adjust psychologically, and go on to develop more chronic mood disorder.

Studies of early (first weeks) screening have tended to focus on cross-sectional prevalence with no follow-up.(305, 306) However, with transient problems affecting results(15, 307), illustrated by the findings of chapters 3 and 4, an acute screening strategy could overburden services by detecting problems that require no follow-up or intervention.

Given this uncertainty, this pragmatic clinical study was designed to:

- (i) Investigate feasibility of brief screening tests for depression/anxiety assessment in an acute stroke setting.

- (ii) To determine the stability and diagnostic accuracy of early screening for clinically significant depression/anxiety problems at one month post-stroke.

It is recognised the one month follow-up is a short period of time in terms of psychological recovery, post-stroke. However, we adopted this time frame in an attempt to explore the earliest time post stroke in which interventions to aid adjustment and minimise likelihood of mood disorder could be feasibly addressed, thus limiting the potential long term effects on recovery.

4.2. Methods

4.2.1. Participants

I assessed consecutive adult (≥ 18 years) stroke patients admitted to a teaching hospital acute stroke unit (ASU). This ASU directly admits all suspected stroke with no exclusions on the basis of pre-stroke impairments. For this assessment of feasibility, I was deliberately inclusive, but did not include subjects with active diagnosis of major psychiatric disorder (i.e. disorders which would affect consent and understanding such as schizophrenia, bipolar disorder). I included stroke (ischaemic and haemorrhagic) and transient ischaemic attack (TIA) but not subarachnoid haemorrhage. Final cerebrovascular diagnosis was clinical, based on all available data, and made by adjudication panel comprising stroke physicians and radiologists.

Recruitment took place between December 2012 and April 2013. Patients were initially assessed for suitability, including capacity to consent, by the treating clinical team. This medical assessment did not follow a protocol, rather the treating clinical team made an initial decision of whether the patient was medically stable for an attempt at depression/anxiety screening. Suitable patients were approached and consented by myself. I aimed to perform assessments on day of ASU admission.

4.2.2. Assessor

I collected screening and follow-up assessment data. I was trained prior to the study in test delivery by a consultant Stroke Psychologist (Dr Niall Broomfield). This involved: familiarisation, informal practice with the assessments and instructions alongside supervised administration of the assessments to establish a standardisation in their execution.

4.2.3. Assessments

I used depression/anxiety-screening tools validated for use in stroke-survivors. My choice of tool was based on the previous review work (chapter 2), perceived suitability for the acute setting and availability within the trust. The primary focus was mood. I used two depression/anxiety screening tools, one standard depression/anxiety assessment: Hospital Anxiety and Depression Scale (HADS)(197) [GL Assessment] and one potentially suitable for patients with aphasia: Depression Intensity Scale Circles (DISCS)(308).

HADS is a self-report multiple-choice measure of depression and anxiety. The structure and purpose of HADS is discussed in chapter 1.

The DISCS test was developed to screen for depression in patients with cognitive or communication impairment following brain injury. It has been validated within a hospital setting, including stroke.(308, 309) The test comprises a vertical scale of six circles (controlling for visual-spatial disturbances) with increasing levels of shading, representing participant depression levels. Scoring is from 0 “no depression” to 5 “severe depression”. A score of $\geq 2/5$ is defined as “screen positive depression”.(308)

The reference standard for HADS and DISCS was one-month follow-up assessment clinical diagnosis of depression/anxiety disorder. I employed the Mini International Neuropsychiatric Interview (MINI), a multi-component, semi-structured psychiatric questionnaire(310) based on the Diagnostic Statistical Manual of Mental Disorders

(DSM)(121) and International Classification of Diseases (ICD)(311) diagnostic criteria. Telephone administration has been previously validated.(312) I assessed only the mood components of MINI: major depressive disorder and dysthymia (classified together as depression); panic disorder with/without agoraphobia; social anxiety disorder; generalised anxiety disorder (classified together as anxiety) and no mood disorder.

4.2.4. Cognition

Recognising the complex relationship between cognition and depression/anxiety, and how cognition can affect screening, I also assessed patients' cognitive function using a single cognitive screen, the MoCA(161), at baseline and follow-up. A modified MoCA for telephone use (274) is described and showed promise in my systematic review. I used this telephone MoCA (TMoCA) for my telephone follow-up assessments. The TMoCA excludes assessment of visuospatial skills and naming visual cues and score is modified accordingly. The full MoCA rather than the visually impaired version was employed at baseline to allow a full assessment of patient's abilities and to consider the feasibility of administering a multimodal cognitive assessment, which included motor and visual skills Total MoCA<26 was recorded as "screen positive cognitive impairment"(161); (<18/22 for TMoCA).(274) To allow direct comparison of MoCA and TMoCA I described scores as a percentage of total score. In relation to prior findings in previous chapters, I planned to investigate the effect of varying MoCA cut-offs on predicting follow-up cognitive impairment.

4.2.5. Data Collection

I kept a log of total numbers of admissions and reasons why participants were inappropriate for assessment. I also recorded baseline demographic and clinical details to a pre-specified and piloted proforma. Order of testing DISCS or HADS was randomised (coin toss). Scores for HADS; DISCS and MoCA were shared with

patient's clinical team and General Practitioner. Assessments were not modified for patients with specific impairments. Problems that impeded or prevented test completion and instances where I had to provide assistance were noted.

I performed follow-up telephone based assessments at one month post-stroke. Patients gave a preference to morning or afternoon calls at time of consent. Contact was attempted 3 times maximum. Times and reasons for disrupted response was recorded. In the event of no response, the hospital database was checked to ensure the participant was not currently an inpatient. For participants still in-patient, assessment was completed face-to-face on the ward. An option for face-to-face assessment was also given for subjects with no telephone access or who were uncomfortable using the telephone. Order of telephone assessment was fixed: MINI; HADS; TMoCA. I decided to administer the MINI over the telephone to reduce patient burden and following previous research adopting this approach. MINI employs a simple yes or no response format incorporating additional questions to any positive screen responses. Thus, piloting and subsequent experience suggested it lended itself well to use via the telephone.

4.2.6. Analysis

Outcomes of interest were feasibility; stability and test accuracy.

To assess feasibility I described proportions completing screening tests (aided and unaided) and reasons for non-completion, illustrated by flow diagram (Figure 5-1). As my study was designed to test feasibility, I did not pre-specify a target number for inclusion, rather I specified a fixed time period for data collection (4 months).

Our primary test accuracy analyses compared acute depression/anxiety screening tests against one-month clinical diagnosis of depression/anxiety disorder. I created standard 2x2 tables and calculated sensitivity, specificity, positive and negative predictive values with corresponding 95% confidence intervals (95%CI).

I assessed agreement between HADS and DISCS at baseline by comparing proportions assessed as screen positive for depression using a chi-squared analysis.

To assess temporal change in screening tests over time I created a plot of values for repeated measure on vertical axis against time on horizontal axis (“spaghetti plot”) and with Wilcoxon paired tests.(313)

Although not conforming to the classical index test/reference standard paradigm I assessed “accuracy” of early MoCA against “diagnosis” of cognitive impairment using follow-up TMoCA and described results with usual test accuracy metrics. My systematic review has suggested that the standard <26/30 MoCA cut point may be unsuitable for stroke cohorts.(165, 166, 280) I explored the effect of varying MoCA cut-offs on prevalence of “screen positive” cognitive impairment at baseline and follow-up.

All statistical analyses were performed using SPSS version 18.0 (IBM, USA) and Statsdirect software version 2.7.9 (Stats Direct Ltd, UK).

My study was adopted by the Scottish Stroke Network and approved by our local research ethics committee (West of Scotland Research Ethics Committee 1: 12/WS/0275) (Appendix F).

4.3. Results

4.3.1. Participant characteristics

Over the four month recruitment period, 146 patients were admitted to the acute stroke unit; 39 were too unwell to approach; 5 violated inclusion criteria; 102 were approached with 33 refusing screening and 69 recruited.(Figure 4-1).

Recruited subjects were: n=41 (59%) male; median age:71 (IQR:61-81); median NIHSS:3 (IQR:2-5); 41% (n=28) prior stroke; 13% (n=9) prior depression. All subjects with prior depression were prescribed antidepressants, mostly selective serotonin reuptake inhibitors (Fluoxetine (n=6); Dosulepin (n=1); Imipramine (n=1); Setraline

(n=1) and Trazodone (n=1)). Stroke classifications in recruited patients were LACS (n=15, 22%); PACS (n=32, 46%); POCS (n=6, 9%); TACS (n=5, 7%); TIA (n=8, 12%) Median time to screening assessment was 2 days post admission (IQR:1-4).(Table 4-1)

I described selected demographics (sex and stroke subtype) of those who did not agree to testing by using monthly aggregate data that is collected as part of the Scottish Stroke Care Audit (SSCA) and NHS performance targets (HEAT targets) . Both are national quality improvement programmes that collect data to allow 'systematic, comprehensive audit of management and outcome providing feedback through regular reporting and annual review of performance against national stroke care standards'.(314) Monthly data are collated and shared with treating clinical teams. My clinical supervisor was able to derive certain descriptors by subtracting data for those involved in the project from the aggregate figures.

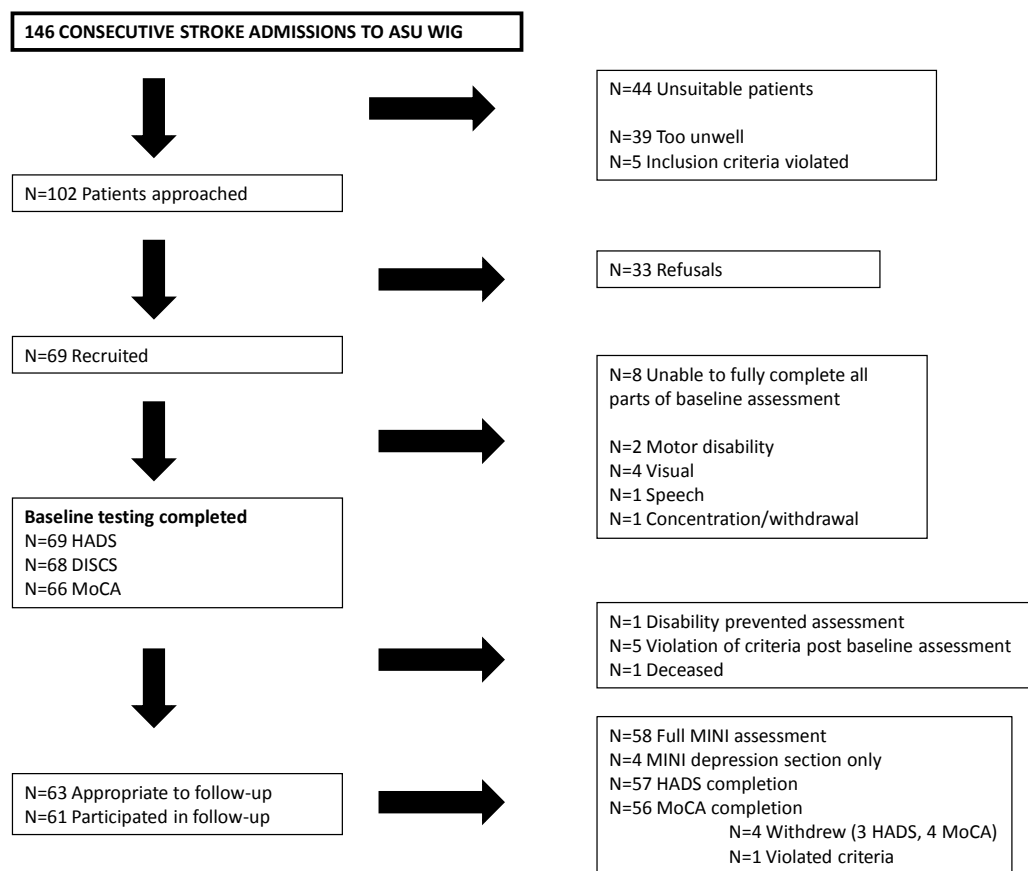


Figure 4-4-1 Flow chart of patient recruitment and assessment

WIG: Western Infirmary General; ASU: Acute Stroke Unit; HADS: Hospital Anxiety and Depression Scale; DISCS: Depression intensity Scale Circles; MoCA: Montreal Cognitive Assessment; MINI: Mini International Neuropsychiatric Interview

Table 4-4-1 Baseline clinical and demographic information

	Total Admitted	Recruited	Not Included
Total	146	69	77
n(%) #	-	(47%)	(53%)
Age	75	71	-
Median (IQR)	(63-83)	(61-81)	-
Males	81	41	41
n(%group) #	(55%)	(59%)	(53%)
Ischaemic stroke	112	57	55
n(%) #	(77%)	(83%)	(71%)
Left hemisphere	64	25	-
n(%)	(44%)	(36%)	-
TACS	30	5	-
n(%)*	(21%)	(7%)	-
TIA	18	8	-
n(%)	(12%)	(12%)	-
NIHSS	4	3	-
Median (IQR)*	(3-8)	(2-5)	-
Prior strokes	-	28	-
n(%)	-	(41%)	-
Prior depression	-	9	-
n(%)	-	(13%)	-

*= significant difference between recruited/not included groups at a significance level of $p < 0.0001$

= Data of non-included patients were calculated from aggregate ward data collected as part of the national stroke audit

† IQR: Inter Quartile Range; TACS: Total Anterior Circulation Stroke; TIA: Transient Ischemic Attack.

4.3.2. Feasibility

All (n=69) participants completed HADS at baseline, n=36 (52%) were able to self-complete the test; n=31 (45%) requested verbal administration and required my input for completion; n=2 (3%) required that I mark answers only. One patient was unable to complete DISCS due to visual impairment with all others able to self-complete. Two did not attempt MoCA (n=1 withdrew after consent; n=1 unable due to stroke impairments). Certain subjects could only partially complete MoCA (n=8, 12%) due to impairments of: vision n=4 (6%); motor skills n=2 (6%) and language n=1 (2%).(Figure 4-1).

4.3.3. Baseline depression/anxiety

Using standard cut-offs (≥ 11), HADS described an anxiety presence of n=11 (16%) and depression n=9 (13%); DISCS described depression in n=25 (37%), with differences between proportions screening positive for depression comparing HADS and DISCS ($p=0.021$).

4.3.4. Follow-up depression/anxiety

Of 69 recruited at baseline: n=63 (91%) were appropriate to contact at one month, with n=61 (97%) participating in follow-up assessment. I collected MINI data from n=58 (95%) (n=4 [6%] completed depression questions only). I collected follow-up HADS data from n=57 (93%). Median time from stroke to follow-up assessment was 36 days (IQR:30-43).(Figure 4-1).

Using standard diagnostic cut-offs MINI defined n=12 (20%) with depression; n=6 (10%) with anxiety disorder.

HADS anxiety and depression subscales both showed poor sensitivity but good specificity for prediction of relevant depression/anxiety disorders at one month.

DISCS demonstrated good sensitivity and specificity for predicting clinical depression at one month.(Table 4-2).

I assessed accuracy of follow-up HADS against corresponding depression/anxiety disorders. One month HADS anxiety and depression subscales had low sensitivity and high specificity (0.92, 95%CI:0.82-0.97; 0.96, 95%CI:0.86-0.99).

Comparing baseline and follow-up HADS anxiety (HADS-A) and depression (HADS-D) scores showed decrease in anxiety (Median:-4, 95%CI:1.20-3.72, $p<0.0001$) and depression scores with time (Median:-2, 95%CI:0.28-2.85, $p=0.04$). (Figures 4-2 and 4-3).

Table 4-2 Accuracy of screening tests for one month mood disorder

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
HADS-A Baseline ≥11	0.17 (0.03-0.56)	0.85 (0.73-0.92)	0.11 (0.02-0.44)	0.90 (0.78-0.96)
HADS-D Baseline ≥11	0.25 (0.09-0.53)	0.94 (0.84-0.98)	0.50 (0.19-0.81)	0.84 (0.72-0.91)
DISCS Baseline ≥2	0.92 (0.65-0.99)	0.78 (0.64-0.87)	0.50 (0.31-0.69)	0.97 (0.87-1.00)
HADS-A Follow-up ≥11	0.33 (0.10-0.70)	0.92 (0.82-0.97)	0.33 (0.10-0.70)	0.92 (0.82-0.97)
HADS-D Follow-up ≥11	0.33 (0.12-0.65)	0.96 (0.86-0.99)	0.60 (0.23-0.88)	0.89 (0.77-0.95)

MINI: Mini International Neuropsychological Interview; 95% CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale Depression subscale; DISCS: Depression intensity Scale Circles; PPV: Positive Predictive Value; NPV: Negative Predictive Value. The grey shaded rows represent accuracy of HADS performed at one-month follow up.

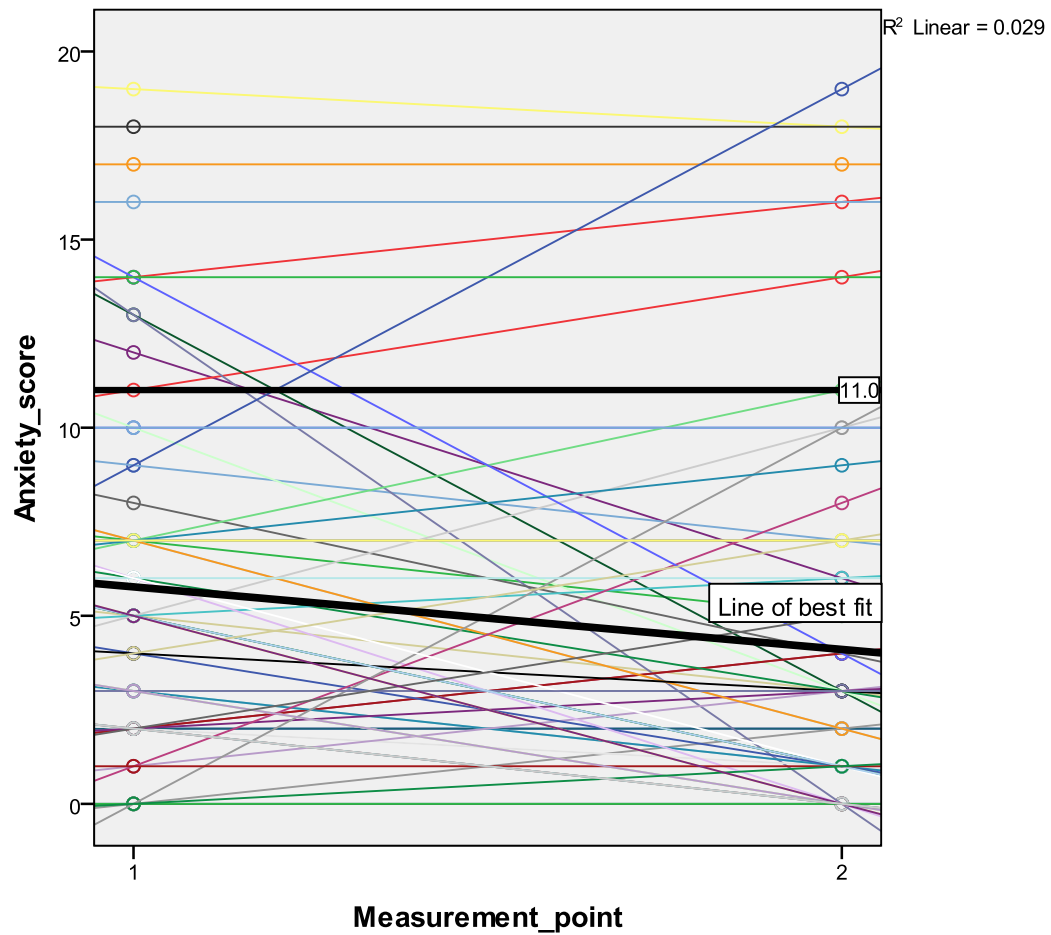


Figure 4-4-2 Graphical display of HADS anxiety scores at baseline and follow-up

Measurement point 1= baseline HADS-A score; measurement point 2= follow-up HADS-A score, the bold line represents the screen positive cut-off.

HADS-A: Hospital Anxiety and Depression Scale Anxiety subscale

Case positive (diagnostic cut off $\geq 11/21$): baseline n=11 (16%); follow-up n=6 (11%)

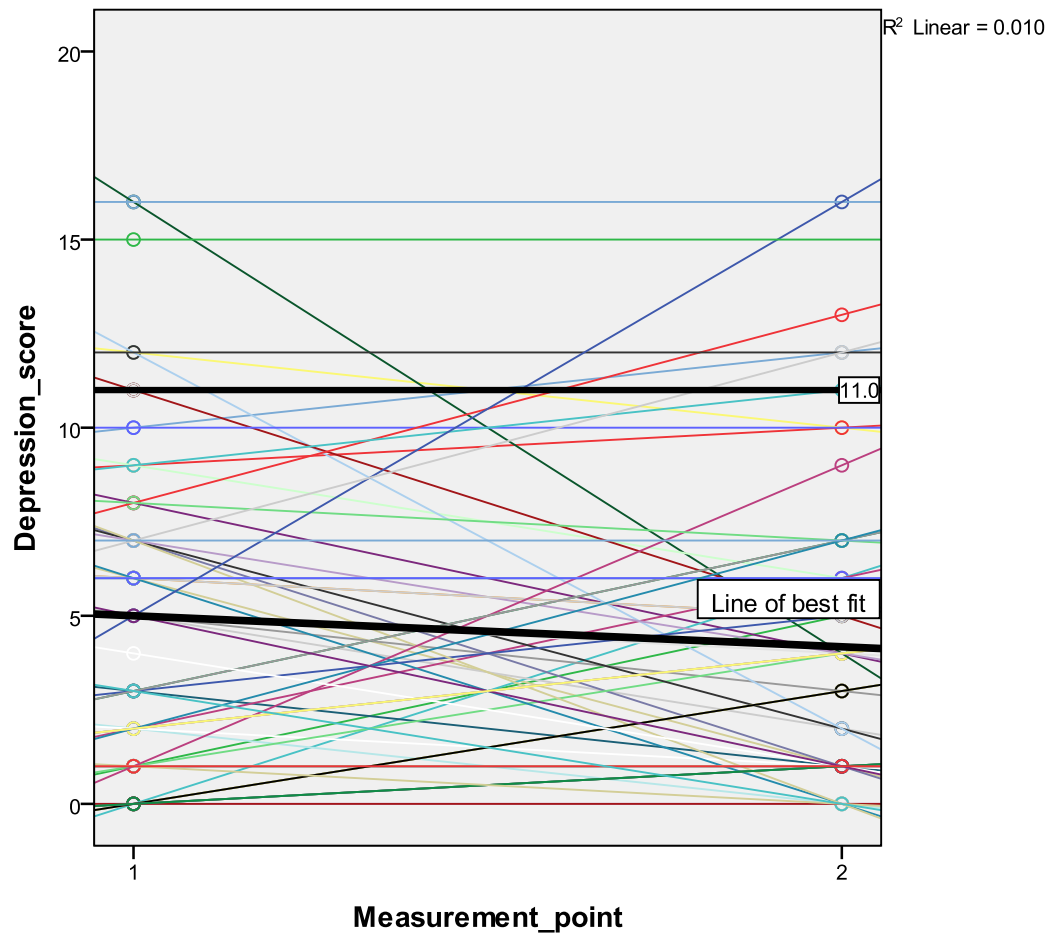


Figure 4-4-3 Graphical display of HADS depression scores at baseline and follow-up

Measurement point 1= baseline HADS-D score; measurement point 2= follow-up HADS-D score, the bold line represents the screen positive cut-off

HADS-D: Hospital Anxiety and Depression Scale Depression subscale.

Case positive (diagnostic cut off $\geq 11/21$): baseline n=9 (13%); follow-up n=5 (9%)

4.3.5. Effects of varying HADS cut-off

At baseline, my detection rate for mood problems using the HADS was lower (n=9 depression and n=11 anxiety) than described in other studies. Along with a low sensitivity and high specificity (compared to MINI outcome at one month) of baseline measures, this suggests that perhaps the cut-off for HADS (as discussed in chapter 1), in such an acute stroke setting is too high. I investigated the effect of varying the screening cut-off for ELEVATED depression and anxiety symptoms.

For baseline HADS-D and HADS-A a cut off of $\geq 7/11$ appears to have the best sensitivity, specificity and predictive values to MINI detection of clinical mood problems at one month. (Tables 4-3 and 4-4)

For HADS measured at one-month follow-up in comparison to MINI outcome at one month: the HADS-D subscale with a cut-off point of ≥ 8 , ≥ 9 or $\geq 10/11$ has the same accuracy. However, performance is best for $\geq 8/11$ for HADS-A subscale. (Tables 4-3 and 4-4).

Overall sensitivity is still lower than specificity in HADS at both baseline and follow-up measurements.

**Table 4-3 HADS-D baseline and follow up subscale test positive vs. MINI
depression case positive for various cut points**

Cut point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
HADS-D Baseline				
≥7	0.583 (0.32-0.81)	0.755 (0.62-0.85)	0.368 (0.19-0.59)	0.881 (0.75-0.95)
≥8	0.50 (0.25-0.75)	0.857 (0.73-0.93)	0.462 (0.23-0.71)	0.875 (0.75-0.94)
≥9	0.333 (0.14-0.61)	0.878 (0.76-0.94)	0.40 (0.17-0.69)	0.843 (0.72-0.92)
≥10	0.333 (0.14-0.61)	0.878 (0.76-0.94)	0.40 (0.17-0.69)	0.843 (0.72-0.92)
HADS-D Follow-up				
≥7	0.667 (0.35-0.88)	0.875 (0.75-0.94)	0.50 (0.25-0.75)	0.933 (0.82-0.98)
≥8	0.556 (0.27-0.81)	0.938 (0.83-0.98)	0.625 (0.31-0.86)	0.918 (0.81-0.97)
≥9	0.556 (0.27-0.81)	0.938 (0.83-0.98)	0.625 (0.31-0.86)	0.918 (0.81-0.97)
≥10	0.556 (0.27-0.81)	0.938 (0.83-0.98)	0.625 (0.31-0.86)	0.918 (0.81-0.97)

95% CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale Depression subscale; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

Table 4-4 HADS-A baseline and follow up subscale test positive vs. MINI anxiety case positive for various cut points

Cut point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
HADS-A Baseline				
≥7	0.5 (0.19-0.81)	0.692 (0.56-0.80)	0.158 (0.06-0.38)	0.923 (0.79-0.97)
≥8	0.333 (0.10-0.70)	0.769 (0.64-0.86)	0.143 (0.04-0.40)	0.909 (0.79-0.96)
≥9	0.333 (0.10-0.70)	0.769 (0.64-0.86)	0.143 (0.04-0.40)	0.909 (0.79-0.96)
≥10	0.167 (0.03-0.56)	0.827 (0.70-0.92)	0.10 (0.02-0.40)	0.896 (0.78-0.96)
HADS-A Follow-up				
≥7	0.667 (0.30-0.90)	0.824 (0.70-0.90)	0.308 (0.13-0.58)	0.955 (0.85-0.99)
≥8	0.667 (0.30-0.90)	0.882 (0.77-0.95)	0.40 (0.17-0.69)	0.957 (0.86-0.99)
≥9	0.50 (0.19-0.81)	0.882 (0.77-0.95)	0.333 (0.12-0.65)	0.938 (0.83-0.98)
≥10	0.50 (0.19-0.81)	0.902 (0.79-0.96)	0.375 (0.14-0.69)	0.939 (0.84-0.98)

95% CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale Depression subscale; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

4.3.6. Cognition

At baseline, using the traditional cut-off <26 , MoCA defined cognitive impairment was seen in $n=54$ (82%). At follow-up TMoCA data was collected from $n=55$ (92%) with $n=26$ (46%) found to be cognitively impaired. (Figures 4-1 and 4-4).

Baseline MoCA demonstrated good “sensitivity” (0.96, 95%CI:0.81-0.99) and poor “specificity” (0.35, 95%CI:0.20-0.53) for predicting enduring cognitive impairment at one month. The proportion with MoCA defined cognitive impairment using the standard cut-off of MoCA <26 was high at baseline. As there are no available stroke norms, I performed post-hoc exploratory analyses varying the screen positive cut-point of MoCA. With lower-cut points, numbers with screen positive cognitive impairment at baseline decreased. Varying the diagnostic cut-off for MoCA defined cognitive impairment altered the sensitivity/specificity. (Table 4-3).

Wilcoxon paired test of baseline and follow-up MoCA, showed a significant increase in percentage score from baseline to follow-up (Median:4%, 95%CI:-7.12 to-0.52, $p=0.014$). (Figure 4-4-4)

Table 4-5 Effects of varying MoCA test positive cut-off for predictive accuracy at one month follow up of TMoCA

Cut point	Baseline case positive n(%)	Sensitivity (95% CI)	Specificity (95% CI)
<26	54 (82%)	0.96 (0.81-0.99)	0.35 (0.20-0.53)
<25	47 (71%)	0.92 (0.76-0.98)	0.52 (0.34-0.69)
<24	45 (68%)	0.89 (0.71-0.96)	0.55 (0.38-0.72)
<23	38(58%)	0.73 (0.54-0.86)	0.55 (0.38-0.72)
<22	34 (52%)	0.69 (0.50-0.84)	0.72 (0.54-0.85)
<21	22 (33%)	0.54 (0.36-0.71)	0.93 (0.78-0.98)
<20	21 (32%)	0.54 (0.36-0.71)	0.93 (0.78-0.98)

**MoCA: Montreal Cognitive Assessment; TMoCA: Telephone Montreal Cognitive Assessment; 95% CI: 95% Confidence Interval.*

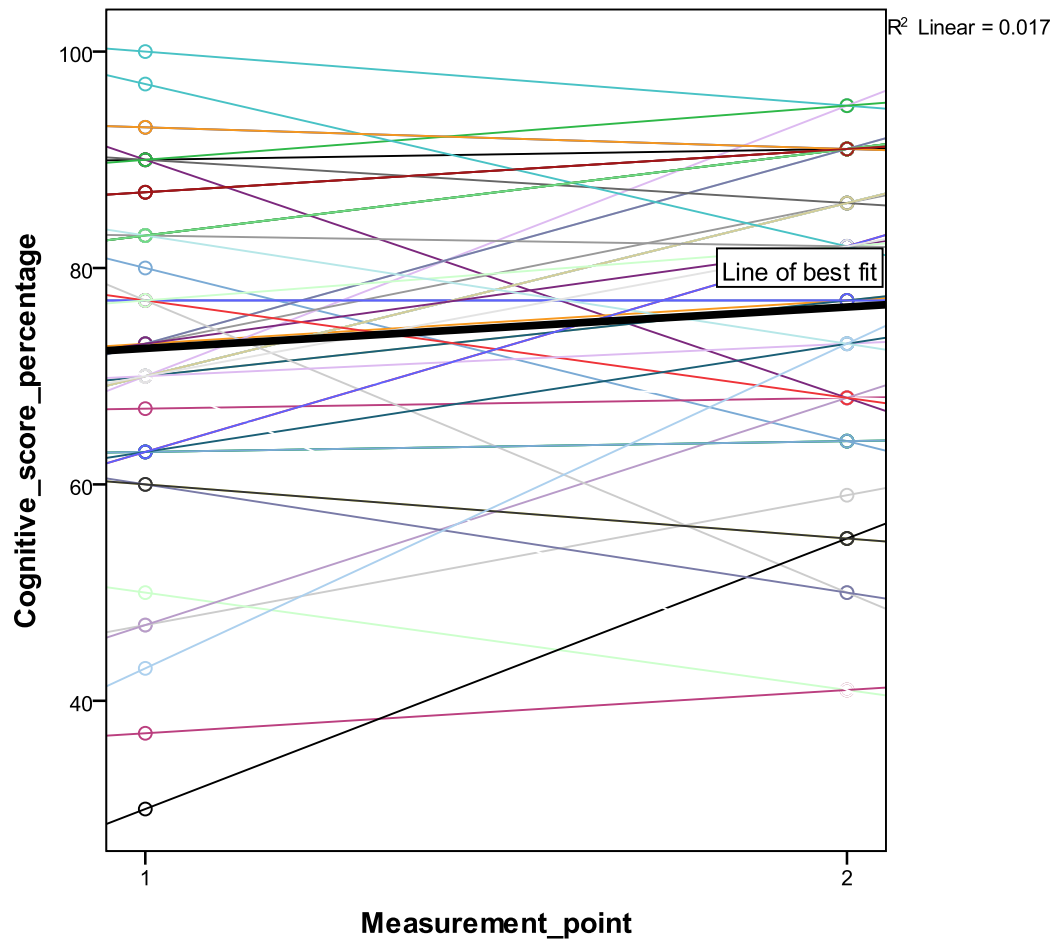


Figure 4-4-4 Graphical display of MoCA baseline and follow-up

Measurement point 1= baseline MoCA; measurement point 2= follow-up TMoCA with the bold line representing the line of best fit.

MoCA: Montreal Cognitive Assessment; TMoCA: Telephone Montreal Cognitive Assessment

Case positive: baseline (diagnostic cut off <26/30) n=54 (82%); follow-up (<18/22) n=26 (46%)

4.4. Discussion

This work sought to explore feasibility, stability and diagnostic test accuracy of depression/anxiety screening in the first days following stroke.

These data suggest that screening *all hyperacute* stroke admissions is not feasible. Less than half of all admitted “medically stable” stroke admissions took part in assessments. I found poor agreement between the acute screening tools and evidence of substantial change over the first weeks post-stroke. Thus commonly used screening tools (HADS) may not be useful for suggesting sustained and clinically important depression/anxiety disorders. However, by lowering the cut-offs for HADS subscales, sensitivity, specificity and predictive values improved in both baseline and follow-up measurements. Thus, HADS may require a lower cut-off in stroke cohorts of $\geq 8/11$ for depression and anxiety subscales, in order to be able to detect clinically important mood problems. The HADS cut offs of 7/8 adopted were based on a-priori decision-making, and guided by the psychiatric literature standard, and local clinical practice. I acknowledge the lower stroke adjusted cut-offs highlighted as appropriate for stroke use in some of the extant literature, but also recent work examining prevalence of post-stroke depression and anxiety which relied on 7/8 cut off approach employed here. There has also been evidence that factorial analysis of HADS cut-off from 8-11 is recommended for identifying probable abnormal levels of anxiety and depression symptoms in brain injury populations.(203, 204, 315)

Assessment feasibility is an important metric if screening is introduced to a busy clinical service. Of the total population, a substantial number were deemed unsuitable for assessment. This is not a concern as the utility of attempting direct screening assessments in medically unwell patients is limited. Those suitable for assessment were mostly able to complete screening tests, although many required assistance. Thus, even using self-completion tests, stroke screening may require input from staff, bringing associated opportunity cost. The proportion of stable patients approached who did not want to participate was unexpectedly high, reminding me not to assume that screening is acceptable to all, however as

mentioned before, this could be due to the lack of benefits from research participation. Future work should focus on qualitative descriptors of patient and staff opinions on neuropsychological screening.

My analyses suggest that tools may have differing properties; with poor agreement between my two screening test strategies. DISCS appears to have most favourable accuracy for predicting clinically important depression at one month. The ease of DISCS administration may explain why it performs well in the acute stage where cognitive impairment is prevalent. My analysis of baseline and one month depression/anxiety scores shows change over time. Generally the trend is for improvement. However there is substantial heterogeneity with some participants improving and some worsening. This pattern makes intuitive sense, diagnosis of a major illness may cause substantial, transient depression/anxiety symptoms for some while others may not develop depression/anxiety problems until they return home and realise the extent of impairments.

MoCA defined cognitive impairment was highly prevalent at the acute stage. As there are no clearly defined norms for acute stroke cohorts, I used the standard cut-point for baseline MoCA (<26). These data suggest that MoCA scores may improve over the first weeks post-stroke. This is consistent with previous research in the post-acute phase where, cognition improves over time and recovery varies across domains.(15, 73, 74) My data suggest that MoCA acute impairment may be transient and lowering the MoCA cut-point may be required to detect clinically important cognitive problems.

As MoCA defined cognitive impairment was significant at the acute stage, this may explain poorer HADS to DISCS performance. Integrating four-choice responses, HADS places a larger demand on working memory than DISCS.

The novelty of this work derives from not only the acute administration of the assessments but from the comparison of the verbal multiple-choice test with non-verbalised one question pictorial test (an assessment designed and validated for brain injured patients). I can therefore look into what is an appropriate format of test at the acute stage, taking into account other complications of the stroke.

Feasibility of administration and within subject performance of these formal screening assessments has not been investigated previously. In addition, by following patients up at one month with a structured interview, I can track changes or improvements, to make inferences about effects of the acute stage post-stroke on the tests and on their ability to be administered to patients.

This work is different from other papers in that most published studies have assessed index test and reference standard concurrently. In contrast, I delay the reference standard to one month and repeat the index test at that point. Therefore it is both a predictive and a one-point test accuracy study. I chose this format to investigate feasibility during the acute stage and to gauge persistent mood disorders. A follow-up assessment with a clinically structured interview at one month allows for this. I can compare assessment outcome at the acute stage with repeated scores at follow up. I can also consider accuracy versus the structured clinical reference standard. In doing so, the potential for transient issues causing ‘white noise’ to assessments can be accounted for.

I acknowledge limitations of this work. The sample may not be entirely stroke representative; more severe strokes were less likely to be included. However it is debatable whether very severe stroke patients would be included in early depression/anxiety screening programmes. Unavailable during study design was a DISCS equivalent for anxiety, although recently one has been published.⁽³¹⁶⁾ I recognise that MINI is not a substitute for clinical (neuro)psychological assessment. For this study I did not seek to describe potential diagnosis underlying a mood disorder rather we collated all within the rubric of “depression” or “anxiety”. Although I was not blinded to individual test scores, a long period had passed before I reassessed patients and I did not have access to scores at the time of doing the follow up assessments, which decreases potential bias. I recognise that the one month follow-up is still relatively early and depression/anxiety may continue to change, however it mirrors other protocols⁽²³⁸⁾ and allowed timely study completion.

This study's strength is the acute assessment paradigm, measuring patient characteristics at a very early stage post-stroke and using commonly employed screening tools. My methodology was necessarily pragmatic and I hope these data may help inform service planning around depression/anxiety screening in stroke. My inclusive recruitment should ensure generalisability and my follow-up rates were relatively high for a prospective observational study.

Future research is required to build on this pilot work. It will be important to observe whether other brief depression/anxiety assessments with minimal cognitive load are feasible for use in acute settings. There is evidence to support brief scales post-stroke, such as the Yale Single Question(208) and Patient Health Questionnaire(317), although not at the acute stages.

Based on these findings, I recommend when assessing mood at the acute stage that a simple assessment wherein cognitive demand is low (e.g. DISCS) be used. I also suggest that MoCA may require a lower cut-off, if used to screen for sustained cognitive problems in stroke.

In addition, given the poor level of acceptability, uptake amongst stable stroke patients and changing test values over the first weeks, adopting a delayed depression/anxiety screening strategy (several weeks post-stroke) when a more stable measure can be made and a higher level of assessment tolerance ensured would be preferred. Our study had an acute assessment focus. National and local guidance recommends assessment during the hospital admission with stroke, which can often be only a few days. In terms of ease of access to patients and availability of staff to perform assessment, the acute setting seems attractive for early assessment of cognition and mood. However, as our results demonstrate there are feasibility issues with acute testing and initial scores on test are highly variable over the first days to weeks. If mood assessment was delayed to the patients' 3-month review, it is likely to have recovered from confounding impairments affecting assessments such as poor concentration, impaired executive function and fatigue. This may allow for patients to complete more of the assessments themselves and give more accurate responses, assuming that providing a verbal response would lead

to patients giving a more positive response so as not to feel judged. Through helping patients complete assessments and reassuring them throughout completion, this should have minimised the impact this had on these assessments for this study. Nevertheless the benefits of assessing patients at such a hyper acute stage is likely to allow for more patients to be screened allowing for potential problems impacting on recovery. As HADS has demonstrated poor predictability at this stage, other assessments may be more accurate, such as the GDS, which has validated shorter versions. With a significant number of patients refusing to take part, this poor apparent acceptability to assessments might be more towards taking part in research rather than the assessments themselves. Separation between acceptability to research and assessments themselves would be difficult to investigate out with the research setting until assessments are performed as part of usual care. Investigations into the feasibility and accuracy of cognitive and mood assessments are needed to further support this work.

Chapter 5 Test accuracy of a short cognitive screening test: The Cog-4

Building on evidence presented in previous chapters

Findings from chapter 2 show preference for brief screening assessments in research and usual practice. In contrast chapter 3 demonstrated few studies investigating very brief measures. Furthermore, each of the previous chapters has demonstrated a need for accurate acute assessments. Chapter 3 found that as specific assessment the Cog-4 test for dementia and had reasonable accuracy for detecting dementia in stroke cohorts.(267) This laid the foundation for assessing its accuracy in an acute stroke setting.

I therefore aimed in this chapter of work to directly investigate the accuracy as and validity of this assessment in the acute stroke setting.

5.1. Introduction

Stroke-survivors with cognitive deficits may have improved outcomes if diagnosis is made at an early stage. Timely diagnosis of potential cognitive issues will allow for appropriate intervention and follow-up.(67) It would be beneficial to both the health professional and the patient if assessments routinely administered could have a multiple purpose.

Few cognitive assessment tools have been specifically designed or validated for use in acute stroke settings as there are many other challenges to overcome.

Cognitive assessment in acute stroke can be complicated by speech disturbance(96) physical impairments and concomitant medical complications including

delirium.(214, 215, 318) A valid assessment of the test properties of the Cog-4 as a screening tool must include subjects' who are representative of those stroke patients likely to be assessed in routine clinical practice. My intention with this work was to mirror "usual practice" through comparison of Cog-4 as a brief tool with a clinically accepted measure in a representative sample of patients examined in the acute stage of stroke.

The National Institutes of Health Stroke Scale (NIHSS) is an impairment scale commonly employed in stroke care. NIHSS assesses neurological function through measurement of; consciousness, language, neglect, visual fields, eye movement, facial symmetry, motor strength, sensation and coordination.(Appendix N)(319) Selected elements of the NIHSS: (1b) orientation, (1c) executive function, (9) language and (11) inattention have been suggested for use together as a short cognitive screening test - the Cog-4. (Appendix O)(267)

The Cog-4 has been shown to provide some indication of cognitive impairment at 18 months post-stroke and superficially assesses cognition after 90 days.(320) Despite these short-comings, there is a possibility that if this brief assessment can be used as a substitute for a screening tool then cognitive implications could be taken from a routine assessment. There is nevertheless evidence that the Cog-4 performs less well than the more detailed screening tool of MMSE.(267) However, the MMSE may not be the ideal comparator, as it has limited ability to describe the executive impairments commonly seen in stroke cohorts.(247, 271) Studies of responsiveness of Cog-4 has suggested that Cog-4 assesses only a limited range of possible cognitive outcomes with a marked 'floor' effect (320, 321) and lacks sensitivity depending on the hemisphere affected.(320, 322) However, other aspects of the Cog-4 are desirable for the acute stroke setting; the assessment is short in duration, does not add to test burden and can be derived from routinely collected data.

I aimed to describe test accuracy and validity of the Cog-4 against a multi-domain, cognitive assessment recommended for all cause vascular cognitive impairment, the MoCA.(22, 161, 166). In specific relation to my study, MoCA was chosen as a

cognitive assessment as its test domains allow for individual component analysis of Cog-4 items, while still offering a valid global test of cognitive function.(166)

The primary aim was to test the accuracy of Cog-4 for detection of MoCA defined cognitive impairment and to describe correlation of individual Cog-4 items and broadly corresponding MoCA cognitive domains.

5.1.1. Methods

The study was devised in line with methodological (i.e. assessment administration) and reporting guidance for diagnostic test accuracy studies, including the dementia specific guidance STARDdem(293, 323) and Quality Assessment of Diagnostic Accuracy Studies - QUADAS2.(262) Although my reference standard was cognitive impairment on MoCA rather than clinical dementia, the best practice described in STARDdem is still applicable to this study.

The Cog-4 is a brief assessment and is unlikely to provide a good alternative to a neuropsychological assessment. However, in order to determine if it can provide meaningful information on basic cognitive function, I chose to compare each item with a corresponding domain on a preferred cognitive assessment tool. This was relatively easy for subscales other than subscale 1c. Although the item is 'commands', it can be justified to assess basic executive function domain based on definitions of executive function. Being able to process verbal information, plan and execute a goal is part of executive processing and thus the command item can arguably be used as a simplistic test of executive function.(324, 325)

5.1.1.1. Data sources

The primary data source was the baseline data collected as part of the acute test study presented in Chapter four. From this study I had access to NIHSS (from which Cog-4 is derived) and contemporaneous MoCA data. To increase my sample size I

pooled my acute test study data with an existing data set that was provided by my supervisor.

This second dataset comprised anonymised data from a previous audit of stroke practice that has been performed as part of the European Hypertension Society (EHS) audit of secondary prevention in stroke. I played no part in collection of the EHS data. A full description of the EHS audit data that was available is in Appendix G and H. In brief, sequential stroke admissions to two acute stroke units (Glasgow Royal Infirmary and Western Infirmary) were included in the audit; trained assessors by took data from retrospective case note review. Training was performed by senior physicians and consisted of implementing and marking assessments as well as reading and extracting data from medical case notes. The EHS included baseline descriptors of NIHSS and MoCA (both were standard measures in participating units at time of the audit). The NIHSS and MoCA data had been collected with scoring of each individual component and so these data were suitable to be pooled with my trial data.

Ethical approvals for the acute mood study are described in Chapter Four. The EHS audit had appropriate approvals from the relevant Caldicott guardian and agreements from clinical leads at both sites. Agreement from the Caldicott guardian that I could use the audit data for a secondary purpose was confirmed (relevant paperwork is included in Appendix G and H)

5.1.1.2. Assessments

The index tests were the subscales of the NIHSS (orientation, executive function, language and inattention) that make up the Cog-4.(267) Each component is scored from 0 to 2 or 3 with >0 being considered abnormal (Appendix N); increasing scores describe greater severity of impairment within that domain.(320) The reference standard was the MoCA. Component domain scores range from 2 to 6 and include: visuospatial/executive function; animal naming; short and long term memory; attention; language; abstraction and orientation.

In Cog-4 elements of the NIHSS are taken as proxies of cognitive domains: NIH 1b orientation; NIH 1c executive function; NIH 9 language and NIH 11 (visual) inattention. I compared with corresponding domains of MoCA. Cog4 and MoCA had certain domains that purported to measure the same construct, orientation, executive function and language; the Cog4 domain of (visual) inattention had no direct equivalent within MoCA and I chose visuospatial function as being closest in nature.(326)

The recommended standard test cut-points of ≥ 1 for Cog-4(327) and $<26/30$ for the MoCA(161) were employed as testing positive for cognitive impairment. Assessments were not modified for patients with specific impairments; however, disabilities that may have impeded scores were noted.

Where no score data were available for the Cog-4 or MoCA, these participants were removed from analysis. The total scores were calculated and classified from available data, where participants were unable to complete a particular section of the test this was scored as 0.

5.1.2. Analysis

My primary analysis was the test accuracy of total Cog-4 for the binary outcome cognitive impairment/no cognitive impairment based on MoCA scores. Secondary analyses described correlation between individual components of the Cog-4 and the corresponding domains of the MoCA. Because of the ordinal nature of these data I used a Pearson correlation to compare domains. I created a 2x2 and 3x3 data table for primary analyses. The 3x3 table allows for those unable to complete testing to be considered in the analysis and should give a better reflection of how the test performs in clinical practice.(295) From these I calculated sensitivity, specificity, positive and negative predictive values with corresponding 95% confidence intervals (95% CI).

I recognised that NIHSS scores favour dominant hemisphere and anterior lesions. The effect of hemisphere on Cog-4 properties has previously been described. On

advice from reviewers I performed post-hoc subgroup analyses, repeating the analysis limited to those with TACS/PACS.

For ease of understanding I collated the data and present all data as pooled (acute study and EHS audit unless otherwise stated).

Statistical analyses were performed using SPSS (IBM, version 19.0, USA), Minitab (Minitab Inc, windows version 15, USA) and Statsdirect software (Stats Direct Ltd, version 2.7.9, UK).

5.1.3. Results

Useable data were available for 173 (n=66 acute mood study; n=107 EHS audit). The majority of participants were able to complete the screening assessments: 166 had Cog-4 data and 148 MoCA (Table 5-1). Some participants were only able to score part of the MoCA, in this instance those domains that could not be scored were coded as zero; this was required in n=12 (7%).

Table 5-1 Test accuracy of Cog-4 and MoCA as "3x3" table

	MoCA + 've	MoCA - 've	MoCA untestable
Cog-4 + 've	45	1	17
Cog-4 - 've	79	23	1
Cog-4 untestable	0	0	7

Cog-4= 4 cognitive areas of the National Institute of Health Stroke Scale, diagnostic cut-off used was $\geq 1/12$

MoCA= Montreal Cognitive Assessment, diagnostic cut-off used was $<26/30$

+ 've = case positive for cognitive impairment

- 've = case negative for cognitive impairment

Stroke classifications by OSCP were: LACS (n=38, 22%); PACS (n=54, 31%); POCS (n=12, 7%); TACS (n=27, 16%); TIA (n=10, 6%); other/unclassified (n=32, 18%). Median total NIHSS was 3 (IQR: 2-6; range: 0-24) and median Cog-4 was 0 (IQR: 0-1; range: 0-8). There were various risk factors for cognitive impairment within subjects: 16 (9%) had a previous diagnosis of dementia; 15 (8.7%) had depression and 26 (15%) had pre-stroke visual or hearing impairments. (Table 5-2)

The MoCA recorded 82% (n=124) of participants with data available, as having cognitive impairment at standard diagnostic cut-off and the Cog-4 recorded 37% (n=62). Test accuracy is described in Table 5-3.

In the individual domain analyses: significant (Pearson) correlations were found for orientation ($p<0.0001$), language ($p<0.0001$) and inattention ($p=0.02$), albeit strength of association was modest $r= -0.44$, -0.37 and -0.19 respectively (Table 5-4).

My post-hoc subgroup analysis suggested test properties of Cog-4 were not improved when the test was limited to those with anterior strokes (TACS, PACS): sensitivity 0.53 (95%CI:0.41-0.65), specificity 0.50 (95%CI:0.46-0.99), PPV 0.99 (95%CI:0.87-1.00), NPV 0.13 (95%CI:0.06-0.28)

As prevalence of MoCA defined cognitive impairment was higher than anticipated, I performed post-hoc analyses describing test properties of Cog-4 at two other cut-off MoCA scores that have been suggested for use in stroke populations. Sensitivity improved with lower MoCA cut-offs but remained suboptimal (Table 5-5).

Table 5-2 Clinical and demographic information of participants

		Participants n(%)	Median	IQR	Range
Participant demographics					
All Data Data set 1 Data set 2	Males	92 (53%) 41 (59%) 55 (50%)	-	-	-
All Data Data set 1 Data set 2	Age	- - -	74 75 71	63-83 63-83 64-85	28-97 28-97
All Data Data set 1 Data set 2	Prior Stroke	70 (40.5%) 28 (41%) n/a	-	-	-
OCSP Classification					
All Data Data set 1 Data set 2	LACS	38 (22%) 17 (25%) 25 (23%)	-	-	-
All Data Data set 1 Data set 2	PACS	54 (31%) 31 (45%) 28 (25%)	-	-	-
All Data Data set 1 Data set 2	POCS	12 (7%) 6 (7%) 8 (7%)	-	-	-
All Data Data set 1 Data set 2	TACS	27 (16%) 5 (7%) 18 (16%)	-	-	-
All Data Data set 1 Data set 2	TIA	10 (6%) 8 (12%) 4 (4%)	-	-	-
All Data Data set 1 Data set 2	Unclassified	32 (18%) 3 (4%) 27 (24%)	-	-	-
Cognitive Impairment Risk Factors					
All Data Data set 1 Data set 2	Dementia	16 (9%) 0 14 (13%)	-	-	-
All Data Data set 1 Data set 2	Depression	15 (8.7%) 9 (13%) 7 (6%)	-	-	-
All Data Data set 1 Data set 2	Visual/hearing impairment	26 (15%) n/a 14 (13%)	-	-	-
Assessments					
All Data Data set 1 Data set 2	NIHSS	-	3 3 5	2-6 2-5 1-5	0-24 1-23 0-24
All Data Data set 1 Data set 2	Cog-4	-	0 1 1	0-1 0-1 0-2	0-8 0-8 0-8

**data set 1= chapter 4 data; data set 2 = chapter 5 data*

OOSP= Oxford Community Stroke project; LACS= Lacunar stroke; PACS= Partial anterior circulation stroke; POCS= Posterior circulation stroke; TACS= Total anterior circulation stroke; TIA= Transient Ischaemic Attack; NIHSS = National Institute of Health Stroke Scale; Cog- 4= 4 cognitive areas of the National Institute of Health Stroke Scale; n/a: data not collected

Table 5-3 Test accuracy comparisons between total Cog-4 and MoCA

Data set	Cog-4	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Correlation (r)	Significance (p value)
All data		0.36 0.28 - 0.45	0.96 0.80 - 0.99	0.98 0.89 - 1.00	0.23 0.16 - 0.32	-0.48	<0.0001
1	Estimate (95% CI)	0.26 0.16-0.41	0.92 0.62-1.00	0.23 0.14-0.35	0.77 0.65-0.86		
2		0.58 (0.45-0.69)	0.6 0.39-0.78	0.53 0.42-0.63	0.47 0.37-0.58		

**data set 1= chapter 4 data; data set 2 = chapter 5 data*

Cog-4= 4 cognitive areas of the National Institute of Health Stroke Scale, diagnostic cut-off used was $\geq 1/12$

MoCA= Montreal Cognitive Assessment, diagnostic cut-off used was $<26/30$

**Table 5-4 Correlations and mean scores between sub-domains of Cog-4
and MoCA**

	Cog-4 sub-domain	Correlation (r)	Significance (p value)	Cog-4 Mean (SD)	MoCA corresponding domain Mean (SD)
All data	Orientation	-0.44	<0.0001	0.06 (0.35)	1.99 (1.03)
1		-0.24	0.05	0.41 (0.80)	2.41 (0.51)
2		-0.21	0.04	0	1.90 (1.09)
All data	Executive Function	-0.03	0.72	0.36 (0.68)	2.53 (1.75)
1		-0.29	0.50	0.35 (0.79)	2.59 (1.37)
2		-0.054	0.60	0.36 (0.66)	2.52 (1.83)
All data	Language	-0.37	<0.0001	0.21 (0.50)	4.59 (1.74)
1		-0.21	0.083	0.41 (0.80)	5.00 (1.32)
2		-0.61	<0.0001	0.17 (0.41)	4.51 (1.82)
All data	Inattention	-0.19	0.02	0.20 (0.52)	4.06 (1.89)
1		-0.08	0.50	0.59 (0.87)	4.71 (1.36)
2		-0.02	0.85	0.12 (0.37)	3.93 (1.96)

**data set 1= chapter 4 data; data set 2 = chapter 5 data*

Cog-4= 4 cognitive areas of the National Institute of Health Stroke Scale

MoCA= Montreal Cognitive Assessment

**Table 5-5 Test accuracy comparisons between the total Cog-4 and MoCA
at different cut points**

Cog-4	Sensitivity <20	Specificity <20	Sensitivity <24	Specificity <24
Estimate	0.49	0.86	0.40	0.89
95% CI	0.37-0.60	0.76-0.92	0.31-0.50	0.77-0.95

Cog-4= 4 cognitive areas of the National Institute of Health Stroke Scale, diagnostic cut-off used was $\geq 1/12$

MoCA= Montreal Cognitive Assessment, diagnostic cut-off used was <20/30 and <24/30

5.2. Discussion

I have demonstrated suboptimal validity and test accuracy of Cog-4 as a brief cognitive screening assessment for acute stroke. My analysis showed favourable specificity but at the expense of poor sensitivity. At this stage post stroke, sensitivity is favoured over specificity. It is more important to detect all cases even at the risk of certain patients receiving unnecessary further cognitive assessments. Therefore the Cog-4 is not appropriate for screening with such a low sensitivity. In addition, although total Cog-4 showed significant correlation with MoCA, association was modest. Three individual Cog-4 domains were significantly correlated with corresponding cognitive domains (orientation, language and inattention) although again strength of association was at best modest. My data suggest that many stroke survivors with potential cognitive problems would not be picked up by Cog-4 testing and other brief cognitive screening tests may be better suited to acute stroke. The correlation data suggest that Cog-4 items may not robustly measure the cognitive domains it purports to measure.

These test accuracy data are in keeping with previous research that has described reduced sensitivity of Cog-4 to detect cognitive impairment(267). My analysis was necessarily pragmatic. I recognise that MoCA is not a definitive diagnostic test rather MoCA offers a more detailed multi-domain screening tool. As the Cog-4 is a

superficial measure, I chose the MoCA as the ‘reference standard’ for the Cog-4 as it is a validated screening tool for these domains in the stroke population.

My reference standard, the MoCA, recorded 82% (n=124) of participants, as having cognitive impairment. This is higher than previous study estimates; however previous studies were not performed in my very acute time frame.(280, 328, 329) In the absence of consensus agreement for MoCA diagnostic cut-off in the stroke setting, I used the standard cut-off described for MoCA. The very high prevalence of cognitive impairment recorded suggests that this cut-off may be too high. Other authors have investigated and suggested alternative cut-points(165, 280) which I explored in this chapter and chapter 3 and 4. In agreement with chapter 3 and 4, my post hoc analysis of these data continued to show that lower cut-points in the MoCA improve the properties of the Cog-4 to an extent, but not sufficiently to recommend the use of the Cog-4. The substantial early cognitive burden in acute stroke I have demonstrated is a factor to be mindful of in context of recommendations for cognitive screening in acute stroke and an area that would benefit from further research to describe the incidence and natural history of these early cognitive impairments.

5.2.1. Strengths and limitations

Although consecutive stroke unit admissions were assessed, the median NIHSS is low for an unselected acute stroke cohort as those with very severe stroke were excluded. While this limits generalisability, in practice, standard cognitive assessment in the context of severe stroke or other medical emergency is unlikely to be feasible or clinically useful. Rather I present data on a population representative of stroke survivors who may be considered for acute cognitive screening.

Furthermore, patients approached were assessed under research conditions and not as a requirement for stroke care. This could limit somewhat the generalisability of findings to the clinical population, as patients were able to withdraw or refuse at

any point of assessment. Further, it is possible some patients may not have shown their true capability due to fatigue or lack of interest. Results may have been impacted by this, especially considering the limited scope of treatment/therapy available for cognitive impairment. Furthermore, the assessments were done at a time convenient for the patient and accommodating other MDT care. The level of fatigue and concentration is likely to be affected by the patient having therapy just before or even just the time of day. No data to clarify this were collected. However, with a reasonable sized population involved in data analysis, we can assume that the effect on results will be limited.

Accepting these limitations, I present data on an important, topical and relatively under researched area of stroke care. The size of the dataset is comparable to other test accuracy studies, as seen from chapter 3. As best as possible I took steps to follow best practice in methodology and reporting.

5.3. Conclusions

These data suggest that although cognitive screening within the acute stroke setting is generally feasible, Cog-4 may not be suited to this purpose. In particular Cog-4 may be insufficiently sensitive to detect cognitive impairment in stroke-survivors and certain domains of Cog-4 may not be valid measures of the cognitive constructs they purport to describe.

I have shown that favourable diagnostic properties of “traditional” screening instruments should not be assumed. Given current recommendations for routine cognitive assessments in stroke I would urge further test accuracy assessments of any proposed screening instruments to inform the choice of optimal assessment at various stages of the stroke survivor journey.

Chapter 6 Ongoing research protocol: Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting

Comparison of the Addenbrookes' Cognitive Examination- third edition, Montreal Cognitive Assessment and Mini Mental State Examination

The preceding chapters have indicated that there are many obstacles to overcome in acute screening, in order for assessments to be both feasible and accurate for the majority of stroke patients. Due to assessments being vulnerable to temporary post-stroke deficits, it suggests that screening may be more valuable if administered at a later time.

Brief assessments, despite their appeal for reducing burden on patients and the clinical team, are vulnerable to the problems present at the acute stage. This is the foundation for my on-going work; does brief screening tool feasibility and validity improve after the acute stage to identify impairments? Or is a longer test more appropriate? The following chapter is the protocol to investigate this. This has been approved by the Scottish A Research Ethics Committee (14/SS/0042) (Appendix I) and received a grant from GG&C NHS research endowments fund. I took a leading role in writing this protocol and contributed to the writing of the grant application.

6.1. Feasibility and accuracy of cognitive assessments post-acute stroke

The findings from previous chapters suggest that acute assessments, despite being preferred for initiation of potential early interventions, are likely to be inaccurate unless adjusted to acute stroke obstacles. As demonstrated from chapter 3, screening assessments vary across setting.

Community/outpatient stroke survivors are likely to have fewer cognitive and physical deficits, compared to inpatients on a rehabilitation ward. Presence of physical, language, visuospatial impairments will affect administration and scoring of standard cognitive assessment tools. It is important to understand if the problems with accuracy and feasibility are present in all stages of inpatient care. To address this question and make an informed decision about appropriate assessments and timing of screening post-stroke, I developed and initiated a study investigating cognitive assessments in a rehabilitation ward setting. Not only will this compare short and longer cognitive assessments; it also investigates feasibility, concurrent sensory/physical deficits with the effect of stroke severity on administration and completion. Data collection for this study is on-going and at time of writing I do not have final data to facilitate analyses.

Delaying assessments to later in the stroke journey could diminish the effect of temporary impairments and allow for measures to correctly identify deficits without over adjusting for other impairments.

6.2. Introduction

Stroke cognitive screening is being adopted across many Scottish stroke sites and is required in England and Wales based on the dementia Commissioning for Quality and Innovation (CQUIN) report 2012/13.(30) No stroke specific assessment tools are in common use and or have robust validation data. Assessment in a stroke-survivor

population may pose unique challenges, for example aphasia; concomitant delirium; prevalent dementia; physical and sensory impairments.

Validated and popular neuropsychological tests for assessing cognition within the cognitively impaired and stroke patient populations include: MMSE(22, 31, 158, 244, 330), MoCA (161, 166, 280, 331) and the ACE-R(166, 168-170, 332, 333). All of these tools are currently used in Greater Glasgow and Clyde stroke services, as shown by the questionnaire in chapter 2. They take between 10-20 minutes to administer and can be used by any member of staff after brief training.

Each tool has advantages and limitations. MMSE has been the traditional favoured assessment for all hospital inpatients. However, MMSE is not suitable for the executive problems seen post-stroke(239, 247) as it contains no specific sub-test to assess this domain and, perhaps more importantly, copyright issues are now being enforced that will require hospital trusts to pay for continued use of the scale. As discussed in chapters 3 and 4, MoCA may be better suited to post-stroke assessment than MMSE, but cut-offs may need reviewed in stroke settings.(76) The ACE contained the MMSE and so has been revised in light of MMSE copyright issues. The new ACE-III shows promise but experience is limited particularly in a stroke setting.

We should not base policy on opinion or tradition; we need an evidence base to guide recommendations for cognitive assessment tool(s) in stroke. Thus there is urgent need for studies describing and comparing properties of screening tools. The ideal tool should be quick, acceptable to patient and staff; feasible; reliable and accurate. My aim with this study is to describe feasibility and comparative accuracy of the three assessment tools.

This study will investigate properties of the newly updated ACE-III, the MoCA and the MMSE in stroke on rehabilitation settings (≥ 2 weeks post event). Participants will be recruited from entry into rehabilitation services or ≥ 2 weeks post-stroke.

The aims of the study are: to establish if assessments in usual clinical practice (as suggested by previous survey) can feasibility be employed in a rehabilitation setting, to describe the “cost” in terms of assessor and patient time and to

compare proportions “test positive” at various thresholds across the three commonly used multi-domain assessments.

6.3. Aims and research questions

My goal is to test the properties of ACE-III, MMSE and MoCA in a stroke rehabilitation setting.

I wish to gain experience of testing cognitive assessments in a rehabilitation setting. It is likely that rehabilitation will be representative of the most impaired post-stroke patients and thus will provide the most robust assessment of screening feasibility. The anticipation is that these pilot data will inform an application for a more definitive prospective diagnostic study of various cognitive testing strategies.

Specific aims of this project are:

- To describe feasibility of ACE-III, MMSE and MoCA in a rehabilitation setting
 - How much time it took to administer assessments?
 - Which areas of assessment did patients struggle most in? i.e. what sections were they unable to complete?
 - Proportion of participants able to complete all assessments.
 - Average number of attempts required in order to assess patients
- To “phenotype” confusion in a stroke rehabilitation setting and explore the effect of important confounders (aphasia, delirium, dementia, sensory impairment) on ACE-III, MMSE and MoCA.
- To compare corresponding domains of ACE-III, MoCA and traditional MMSE assessment through correlation.

6.4. Plan, methods, expertise available and statistical power

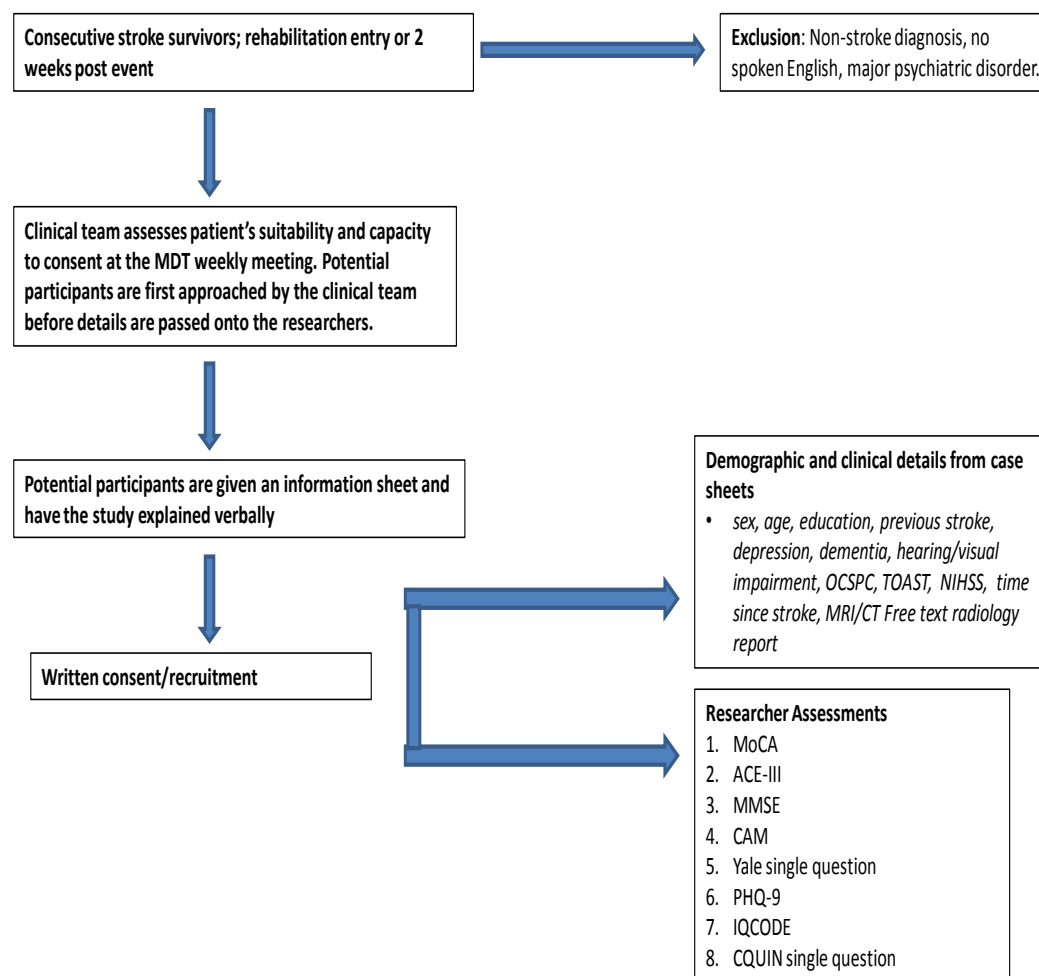
6.4.1. Overview

Consecutive patients will be recruited across two rehabilitation sites (Western Infirmary Glasgow linked with Gartnavel General Hospital and Glasgow Royal infirmary linked with Stobhill Hospital). Gartnavel has a rehabilitation ward comprising of 20 beds and Stobhill 24 beds. The turnover in rehabilitation is between two and four patients per week. Assessment for suitability, including ability to consent, will be made by the clinical team. This information will be shared with the researchers at the weekly multidisciplinary team reviews. The clinical team will check that patients are happy to be approached by the researcher before giving details to the research team. Suitable patients will be approached by researchers (myself and fellow PhD student, Kirsty Hendry). Data collection and assessments will be performed by both of us. We are both psychology graduates with clinical research experience, and have been fully trained in use of all scales by stroke specialist clinical neuropsychologist, Dr Niall Broomfield.

Stroke -survivors and their chosen informant will be provided with an information sheet (PIS) and a verbal explanation of the study (Appendices F-H). If the patient and chosen informant understand and are willing to participate then written consent will be attained. Baseline demographics and clinical details will be extracted from subject's case-sheets. Order of testing ACE-III, MoCA and MMSE will be randomised and split between two sessions to reduce patient burden. Other assessments performed/collected by researchers will include: the Confusion Assessment Method (CAM) for delirium; National Institute of Health Stroke Scale (NIHSS) for neurological function; Patient Health Questionnaire (PHQ-9) and Yale Single Question for Depression; Informant Questionnaire of Cognitive Decline (IQCODE) and Commissioning for Quality and Innovation (CQUIN) single question for a measure of cognitive decline and dementia. This combination will provide a comprehensive picture of the patient. If patients express an interest in their results the researcher performing the assessment will refer the patient to the clinical team, with whom the results will be shared, and they can make a more

comprehensive assessment of performance. In the event that a participant becomes distressed or frustrated and it is clear that they are unable to complete the testing, it will be stopped. Any anxiety or distress from assessment will be handled through reassurance or ending of the assessment. If we detect probable depression, we would advise the clinical team to consider referral to Stroke Neuropsychology service depending on patient preference. If we detect suicidal ideation, the clinical team would be immediately informed and any required risk procedures/crisis management strategies put in place. The researcher would be carefully trained in suicide risk assessment procedures by Dr Broomfield. Participants will have the right to withdraw at any time.

All data will be kept on a password-protected spreadsheet on an encrypted NHS USB that will be kept in a locked cabinet within a clinical base. Hard copies will also be kept within the locked cabinet and neither will leave the clinical premises.



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Figure 6-1 Flow chart of study strategy

MoCA: Montreal Cognitive Assessment; ACE-III: Adenbrookes' Cognitive Examination - Third edition; MMSE: Folstein's Mini Mental State Examination; CAM: Confusion Assessment Method; PHQ-9: Patient Health Questionnaire - 9 items; IQCODE: Informant Questionnaire of Cognitive Decline in the Elderly; CQUIN: Cognitive Informant Question; OCSPC: TOAST: NIHSS: National Institute of Health Stroke Scale; MRI: Magnetic Resonance Imaging; CT: Computer Tomography.

6.4.2. Participants

I am interested in stroke-survivors who still have active impairments but are medically stable, thus I will focus on rehabilitation units. Participants will be adult (≥ 18 years) stroke-survivors (including subarachnoid haemorrhage) patients entering rehabilitation or two weeks from index event, whichever is longer. Participants will be recruited on a consecutive basis and include first and multiple stroke patients, with no limitation on hemisphere location. Kirsty and I will recruit as many eligible stroke survivors as possible over a 5-month period (aiming to recruit around 50 survivors). I have not pre-specified a sample size as one of the metrics of interest in this study is feasibility of recruitment in a rehabilitation setting.

At the weekly multidisciplinary team reviews, the clinical team will identify potential participants and check that these patients are happy to be approached by the researcher before giving details to the research team.

Stroke survivors will be given a patient information sheet (Appendices I, J and K) and verbal explanation of the study. They will be given a minimum of 24 hours to consider the study. Kirsty and I will assess eligible patients once weekly and seek formal consent. Our only exclusions will be: non-stroke diagnosis; major psychiatric disorder; no spoken English.

6.4.3. Standard assessment

6.4.3.1. Primary Measures

1. Addenbrooke's Cognitive Examination 3rd version (ACE-III)

The ACE-III is a slightly longer and more in-depth cognitive assessment compared to the MoCA and MMSE and is described in detail in the introduction.

2. Montreal Cognitive Assessment (MoCA)

MoCA is a multi-domain assessment developed to detect MCI in community dwelling older adults; it has been discussed in detail within the introduction chapter and test accuracy was described in chapter 3.

3. Folstein's Mini Mental State Examination (MMSE)

MMSE is a short cognitive assessment developed to replace neuropsychological batteries in determining the level of patient cognitive impairment. Contents and accuracy are discussed in the introduction and chapter 3.

6.4.3.2. Secondary measures

4. National Institute of Health Stroke Scale (NIHSS)

The NIHSS is measure of neurological deficit after stroke. It has 15 items covering; consciousness, vision (gaze and detection), facial palsy, motor function and ataxia (arms and legs), sensation, language (comprehension/expression, production) and attention.(319) The NIHSS includes assessment of language and can be used as a screen for substantial communication difficulty. If NIHSS is not documented; it will be derived from available information recorded in the case-sheet. Previous work in our department validated this approach.

1. Confusion Assessment method (CAM)

The CAM is a short screening questionnaire for delirium. It was developed to replace assessments that required specific psychiatric training.

2. Patient Health Questionnaire for Depression (PHQ-9)

The PHQ-9 is a multiple-choice questionnaire that screens for depression completed by the patient. It has 9 items relating to behaviours and feelings with an additional rating of how much issues described affect their daily activities item, over the

previous 2 weeks, each scoring 0 (not at all) to 3 (nearly every day). Scores of: 1 to 4 indicate minimal depression; 5 to 9 mild depression; 10 to 14 moderate depression; 15 to 19 moderately severe depression; 20 to 27 severe depression.(334) This takes about 5 minutes to complete.

3. Yale Single Question (YSQ)

The Yale single question (YSQ)(335) for depression was taken from the Yale-Brown Obsessive Compulsive Scale(336). It is a single question: “Do you often feel sad or depressed?” with a ‘yes’ or ‘no’ outcome. It requires little training and does not require the patient to read, write or have normal verbal capabilities.(337) It takes less than 1 minute to complete.

4. Informant Questionnaire on Cognitive Decline (IQCODE)

The IQCODE is an indirect measure of patient cognitive decline over the past 10 years. It is used as a measure of prior function. The details of this assessment are described within the introduction.

5. Commissioning for Quality and Innovation single question (CQUIN SQ)

The CQUIN SQ was developed to raise awareness of cognitive changes rather than as a screening tool to identify at risk patients.(338) This is directed to a caregiver/relative: “Has the person been more forgetful in the last 12 months to the extent that it has significantly affected their daily life?” with the response either ‘yes’ or ‘no’.

Assessments will be performed by Kirsty Hendry and I on the rehabilitation wards.

6.4.4. Data collection

A log will be kept of all admissions and reasons why stroke-survivors were considered ineligible. Basic demographic and clinical details will be extracted from patient case notes and recorded on a standardised proforma. If not available from case notes, a basic examination including screening for aphasia will be performed

using the National Institutes of Health Stroke Scale (NIHSS) and supplemented by screening tests for visual acuity and hearing impairments.

The cognitive assessments will be MMSE, MoCA and ACE-III. Other screening tests included are: for delirium the CAM; cognitive decline or prevalent dementia the IQCODE and CQUIN SQ; neurological function the NIHSS; depression the PHQ-9 and YSQ. At MDT review the team will be asked the question “does this patient have important cognitive impairments?” with a dichotomised yes/no response. All assessments will be paper based and transferred to electronic media. All assessments are currently used and recommended in NHS GG&C, assessment scores will be shared with the treating clinical team.

Assessments will be split between the two sessions; order of assessment and assessor will be randomised. One session will include ACE-III, YSQ and PHQ-9; session two will consist of MMSE and MoCA. The CQUIN SQ and IQCODE are paper-based questionnaires given to family or carers.

Identifiable patient information will not be collected as part of the research. This includes date of birth, contact details or CHI number. Names of participants will only be on consent forms. Assessments will be collated and labelled using participant numbers, no name being recorded. Assessment scores will be recorded in the patients’ medical notes (on the same day of administration) which only the clinical team have access to. All data will be entered to an electronic database, stored on a password-protected document on encrypted USBs that will be kept in a locked cabinet within the clinical base when not in use. Hard copies will also be stored in the locked cabinet and neither will leave the clinical premises.

In addition to the above clinical measures we will collect relevant clinical and social demographic details.

- Sex
- Age
- Education/schooling - based on level reached i.e. secondary school, university etc.

- Stroke classification (oxford community stroke project classification - OCSP)
- Visual and hearing impairment
- History
 - Prior stroke
 - Alcohol dependence
- Days since stroke - based on day of admission
- Hemisphere affected
- Radiological information (reports of any brain imaging performed)
- Neurological function on admission (described using NIHSS)
- Time taken to complete assessments
- Assistance required to complete assessments

6.4.5. Statistical power

For this pilot study I have not performed a sample size calculation; rather I will use data from this study to inform sample size calculations for a future definitive study. Using mean assessment scores, numbers able to provide data for each assessment, participation rate alongside pooled accuracy estimates from chapter 3, I can estimate how many patients will be required to approach, how much time will be required to reach this goal, for future studies in similar populations.

Based on bed numbers, ward turnover and previous recruitment rates a conservative estimate is that we will recruit n=50 over five months.

I will assess feasibility by describing numbers of inpatients; numbers eligible; numbers completing assessments and reasons why assessments not completed. We will compare clinic-demographic details of those completing and not completing assessments. During assessments, researchers will time completion of each test and record if the stroke-survivor needed any assistance to complete.

Using usual diagnostic cut-offs we will describe numbers “testing positive” for each of the three scales and then describe the effect of varying the diagnostic cut-off. I

will specifically test whether domains assessed in the MMSE can be derived from the copyright free tests of ACE-III +/- MoCA. I will describe the accuracy of MDT informal assessment and single question assessments against formal tests.

6.5. Limitations, risks and recommendations

We are assessing a highly selected patient population, stroke survivors requiring patient rehabilitation. This cohort is suited to a study of feasibility. If cognitive testing strategies are feasible in this group with substantial impairments, they should be feasible in any group of stroke survivors. We have struck a balance between information available from test and patient burden. We have chosen to restrict our study to the most commonly used cognitive screening tests. We believe our data will help shape future policy and recommendations regarding cognitive assessment in stroke. Cognitive assessment is recommended for all stroke survivors, so we are not performing unnecessary assessments. I will share all our data with the treating clinical team.

There was also no public involvement in this research design. With no patient input I could have potentially missed important factors around the patient experience of testing.

6.6. Potential impact and dissemination of results

This work is novel in that I am looking into both the feasibility of assessment (completion and administration but also the time required to do so on each participant) in those that are likely to have a mix of physical and cognitive problems but also the feasibility of assessment of participants without capacity through permission of their legal representative, an important concept to look into especially when attempting to generalise about post-stroke recovery.

I anticipate that this work will help inform practice regarding cognitive screening. My meta-analysis of test accuracy suggested that diagnostic accuracy is similar across the commonly used multi-domain cognitive assessment tools. Thus choice of test should be based on other metrics and the most practically important consideration is feasibility and test burden. There is some research considering these issues (37, 41) and when is suitable to intervene and begin rehabilitation.(42) Comparing results between the tests adds to our knowledge of the properties of these tests but may have further utility - given the copyright restrictions on MMSE an important practical question is whether MMSE data can be derived from other sources such as MoCA.

I recognise that these data are pilot in nature and in particular acknowledge that we do not have a gold standard assessment to compare our tests against. I hope that this study will allow us to work towards a grant application for a more definitive study. In which, assessments based on feasibility can be chosen and administered within the rehabilitation setting, cut points altered based on pilot data means and put up against long term follow up (potentially 2 years). The follow-up would consist of a gold-standard neuropsychological assessment as well as daily independence and any scan information already available. This larger based study could provide valuable information on characteristics of those likely to develop dementia or multi-domain cognitive impairments that impact on daily functioning and quality of life. These characteristics can help to identify at risk stroke survivors earlier and therefore provide these patients to potentially benefit from interventions, support or planning for the future. Critical evaluation of the evidence base for cognitive screening tests is of major importance as discussed throughout this thesis.

The results will be shared with practicing stroke clinicians, allied health professionals through the managed clinical networks. In addition the results will be put forward for journal publication and conference presentation.

In my previous work I have established links with stroke Managed Clinical Network and contacts for various local specialist societies (such as the Scottish Stroke Nurses

Forum, Scottish Stroke Neuropsychologists, British Geriatric Society (Scotland), British Association Stroke Physicians, Stroke Allied Health Professionals and Association of Chartered Physiotherapists Interested in Neurology). In addition these works have involved interaction and coordination with various members of the multidisciplinary team. Involving the ward staff in implementation has improved the research as it reduces clashes with usual care and also in finding appropriate times and patients to approach. This gives me a unique opportunity to disseminate these results in a timely and efficient manner.

6.7. Preliminary results

Over the first 3 months we have recruited 34 patients from n=55 medically stable strokes approached (3 refusals, 2 discharged, 14 no capacity and proxy absent with n=34 assessed). The mean number of attempts to speak to consenting patients was 1(IQR: 1-2).

Recruited participants' demographics are: age mean 69years (IQR: 62-84); n=14 males; n=13 left hemisphere; OCSP: n=14 TAC, n=4 POC, n=6 PAC, n=8 LAC, n=1 inconclusive; n=6 haemorrhage; NIHSS mean: 9; mean days since stroke: 44days.

From those assessed n=15 had fully completed ACE-III, n=16 MoCA, n=17 MMSE. (Table 6-1)

Common impairments restricted mainly completion/attempt of drawing tasks especially in the MoCA and ACE-III. The majority of patients were able to complete the MMSE, which also had the lowest completion time. There was a low response rate for informant-based questions due to lack of presence during assessment. The majority of those who responded found their family member to have improved (n=6).

Cognitive assessment in the rehabilitation setting has difficulties in direct administration and completion mainly due to physical impairments preventing

drawing, as well as indirect administration as informants are not regularly available to answer questions.

Cognitive Assessment	Mean Score	Mean time to complete (minutes)	Fully completed assessment n(% of all recruited)	Unable to complete sections n(% of all recruited)	Unknown/not completed or attempted n(% of all recruited)
ACE-III	55	21	15 (44%)	5 (15%)	14(41%)
MoCA	14	10	16 (47%)	9 (26%)	9 (26%)
MMSE	21	7	17 (50%)	6 (18%)	11 (32%)
IQCODE	35	n/a	7 (21%)	n/a	27 (79%)

Table 6-1 Preliminary results of cognitive assessments in rehabilitation

**ACE-II= Addenbrookes' Cognitive Examination 3rd Edition; MoCA= Montreal Cognitive Assessment; MMSE= Folstein's Mini mental State Examination*

Chapter 7 Discussion

Stroke is a prevalent problem. It is responsible for a significant proportion of physical and psychological problems in adults. As psychological issues are not as immediately obvious as physical disabilities, especially among the elderly, assessments that can accurately depict and describe various cognitive domains are needed to allow us to target clinical interventions and effective rehabilitation.

7.1.1. Current application of cognitive and mood assessments

In Chapter two, I aimed to describe the cognitive and mood assessments currently employed in stroke research and in usual practice within stroke care. I hypothesised that as guidelines urge health professionals to assess stroke patients for cognitive and mood problems yet provide no stipulation as to how or when this should be done, there would be a lack of consistency in both research and usual practice over the choice of test.

The data collected supported my hypothesis: not only did I find relatively few stroke publications that included cognitive and mood instruments, but also there was considerable heterogeneity across the measures that were employed within research settings. Thus, as practice should mirror evidence-based research, which provided no clear consensus of test choice, stroke care settings also had poor agreement over which assessment to perform.

Wide variation in assessment poses difficulties when it comes to comparison and description of cognitive and mood impairments across diverse stroke cohorts. Our inability to compare groups reduces our potential knowledge about the true impact of a stroke, including psychological impact, and limits how improvements to recovery can be addressed.

A second relevant finding from the usual practice questionnaire concerned the scheduling of cognition and mood assessment. Cognition testing took priority, was concentrated in the acute stages post-stroke and generally used some form of formal assessment. Formal assessment of mood was deferred until later. It is understandable that mood problems seem easier to observe at the early stages than cognitive deficits; however, as mentioned in chapter one, many mood problems including adjustment affect stroke patients and may manifest with only subtle signs. An incorrect diagnosis/formulation is likely if formal assessment is not employed and has been highlighted in the introduction, neuropsychological (mood and cognition) factors, if undetected, may adversely impact rehabilitation efforts, stroke recovery and patient quality of life.

These findings set a strong foundation towards a need for consensus in measurements. A good area to start would be in test accuracy analysis. An assessment that is not valid, sensitive or specific in identifying impairment is limited in clinical utility. With a strong base of evidence for an accurate assessment, a better understanding of the course/impact of cognitive and mood disorders after stroke could be assembled. In building a fuller picture of stroke recovery, potential interventions can be investigated and a fuller view of their influence on outcomes compared.

Stroke researchers and clinicians are unlikely to be surprised by the findings, it has long been suspected that the stroke clinical community are failing to capitalise on the potential of cognitive and mood assessments.(148, 153) My data provides evidence to support this view and hope it provides further incentive to look towards standardising assessments across studies. I would recommend that stroke researchers produce guidance on preferred outcome measures for cognitive and mood disorders, informed by robust descriptions of test accuracy and clinometric properties of scales in stroke cohorts. This will help to inform this guidance or at least highlight where original research is still needed.

7.1.2. The accuracy of common measures in research

In Chapter 3, I reviewed the published data on common cognitive assessments in order to describe screening tool accuracy for detection of dementia and multi-domain cognitive impairment post-stroke. Based on my findings in chapter 2, I was aware that there may be few papers able to be included in any meta-analysis.

From pooled analysis the data showed that commonly used screening tests performed similarly across studies in terms of accuracy. In addition, pooled analysis did not indicate any significantly superior screening measure to identify all types of dementia or multi domain cognitive impairment. Not surprisingly, I found that according to the cut-offs chosen to identify impairment, sensitivity and specificity varied. As stroke patients have a high prevalence of transient cognitive problems post-stroke, and are usually older with some premorbid deficits, it is likely that sensitivity increases (providing a higher level of those found to be impaired) and specificity decreases (miscategorising patients) when higher cut-offs are employed. I found an improvement of specificity when cut-offs were lowered. This could be because of the effect of potential transient problems affecting performance at the acute stage or stroke patients have a different range of norms than other patient cohorts when testing for cognitive impairments. In support, when the data were split into 'acute' and 'non-acute' settings for comparison, the assessments in the acute settings showed high sensitivity and lower specificity. Within the reverse pattern in the non-acute settings the sensitivity, despite being low, was higher than for the acute settings.

Collection of the entirety of assessment was found to be a crucial issue that would influence measures of test accuracy. Missing sections within tests led to the removal of that patient's assessment from analysis. Poor levels of completion are not only from disability and other impairments but also the extent to which participants are unwilling to complete part or all of the tests. Inability to complete sections due to a confounding disability that does not affect understanding (i.e. difficulty holding a pen) or to a wish to withdraw will lower test score and inflate

estimates of impairments. Feasibility of test administration to patients with varying disabilities should be corrected for when accuracy is being described.

Therefore, these data demonstrated how it is vital for accuracy that cognitive assessments are selected and performed with a particular purpose in mind. The assessments have to be robust in the face of co-existing impairments if we are to gain a clear view of whether deficits will exert a long- or short-term impact.

7.1.1. The prognosis and feasibility of mood assessments in acute stroke

The data from chapters 3 and 4 have indicated that accuracy and feasibility of cognitive assessment performance are susceptible to factors present mainly during the acute stage post-stroke. With potential factors unrelated to impairments preventing patient acceptance for cognitive assessments, it was important for me to investigate if this was also the case with mood assessments. Comparison of verbal and non-verbal assessment allowed me to remove the effect of temporary or lasting cognitive/communication dysfunctions on assessment.

Here again, I demonstrated that not all eligible patients accepted an approach at such an early stage. With the assessments requiring a high level of input from myself for test completion I infer that patients may have concerns around being unable to do a task.

In contrast, the simple non-demanding mood assessment was completed by a higher number of participants and was also more accurate in prediction of mood at one-month follow-up. Cognitive demands appear to play an important role in measurement accuracy across the acute stroke stage.

7.1.2. Accuracy of a regularly administered severity assessment to identify cognitive impairment in acute settings

The results from Chapter 3 suggested that there are limited data not only in acute stroke settings but also regarding very brief screening assessments. Measures of accuracy appear to vary depending on the setting in which screening tests are performed. This may arise perhaps from improvement in impairments over time or in ability to complete the assessment itself (as seen in chapter 4).

Based on the findings of chapter 3, I investigated in chapter 5 how feasible and accurate a cognitive screening tool derived from a regularly administered stroke severity assessment may be in identifying cognitive impairment.

The Cog-4 proved to have modest correlation with corresponding MoCA domains, suggesting that it is not accurate in terms of specific cognitive domain assessment. Although more acute stroke patients had more completed Cog-4 data than MoCA scores, this argument of feasibility and brevity does not allow for accurate assessment of cognitive function.

As discussed within the introduction, there are other confounding deficits that may affect administration of assessment. Therefore some physical deficits may have had an impact on our ability to identify impairments, probably because they influence patients' ability to perform assessment tasks.

Furthermore when considering feasibility, the majority of patients were more likely to complete the shorter less cognitively demanding assessment, the Cog-4. Despite a large response rate to screening, there were still a moderate number of eligible patients who refused to participate or withdrew in the middle of testing without specific reason. This demonstrates that irrespective of potential cognitive, delirium or other deficits, there are other factors at play that affect the feasibility of comprehensive screening within an acute sample. With fatigue commonly affecting stroke patients, along with their potential anxiety of finding another problematic area, these may be one of the reasons why so many refused/withdrew.

7.2. Conclusions

These data have investigated the use of cognitive and mood screening within stroke cohorts. Finding poor consensus in published research and usual practice due to lack of evidence, I investigated common assessments. I found that screening tools had a tendency to vary in accuracy depending on which type of impairment they were being used to detect (i.e. multi-domain cognitive impairment versus dementia) and on the setting in which they were administered.

Furthermore, patient acceptability of assessments was not uniform and the reasons for this were unclear. This could reflect an underlying adjustment problem, an avoidance of potential problematic diagnoses or just poor timing in approaching the patient. Investigation of this could help to improve participation and choice of assessment.

Administration of most assessment tools may achieve greater acceptance during the rehabilitation phase of care but even here the results may be affected by other deficits related to stroke. The study described in chapter 6 is the first step towards investigating this possibility. Through addressing the queries surrounding the balance between appropriate timing and effect of other impairments, the results from chapter 6 could contribute to the expansion of post-stroke cognitive and mood assessment knowledge. The data will hopefully help to lay the foundations for future works of outcome or interventions as a fuller and more accurate picture of patient capabilities can be measured.

Development of protocols (based on these findings) for selecting assessments to detect various deficits and for selecting their timing will render impairment data more comparable across diverse populations. This would greatly strengthen research underpinning future clinical and interventional trials. Comparison of several patient populations using the same intervention improves knowledge of the true effect of that treatment and may let us target interventions toward those who would derive greatest benefits. This will help both individuals and the health care service in terms of time, money and efficient use of limited resources.

As screening is potentially the key to intervention, my findings have importance in the understanding of impairments in cognitive and mood domains and of their

progression post-stroke. However, as discussed in the introduction, there is an argument to be made for screening causing more harm than good in the absence of established treatments for cognitive impairment or dementia. On top of this, current screening tools are far from accurate and it may cause great distress if a patient is stigmatised by being labelled with a deficit or impairment.

From the data that I have collected, conclude that although screening is possible, it may not be accurate during the acute stage unless an appropriate assessment (in terms of administration and format of response required) is chosen. Other researchers recommend various cut-offs for the same assessment across different settings. My data in chapter 3 also reflected this where sensitivity and specificity change between acute and non-acute setting assessment. The assessment also has to be administered when it is acceptable to the patient. The results from this thesis demonstrate that assessments should either be adapted to account for post-stroke impairments which may inaccurately categorise patients, or assessments be chosen based on the patient capabilities. For example a patient unable to move their dominant hand can give verbal responses or a verbally impaired patient provide motor response whether it be pointing or other movements to provide a response. These data should be collaborated and formatted into a flow-chart or similar which allow health care professionals to select appropriate test modalities or the best assessment available for their patient's ability.

From prior studies my acute works show that we are currently finding a higher level of cognitive impairment and mood disorders than previously reported. This could be due to the assessments themselves, the timing or the lack of patients involved in research due to their inability to consent. I was limited to an extent in my clinical research by what kind of patient I could approach and who the MDT thought were appropriate to ask to consent to my research. If there were more treatments/therapies available for cognitive or mood impaired patients at the acute stage, my study design could have been different and included all patients, which would have given a more generalizable view of patient impairment. Although this not an issue for my literature and meta-analysis studies, inclusion for these

data were also limited by what the various authors reported as well as the variability in how, when and what they used in their works.

Therefore, in order for screening to overcome transient problems in the cognitive and mood domains, use of a detailed multi-domain assessment should be better implemented and more meaningful if conducted at a later stage after stroke onset. This may be at follow up appointments, in clinics or in the rehabilitation settings (as I demonstrated with cognitive/mood improvements over one month in chapter 4). These later assessments could be done by any trained member of the clinical team and therefore could represent the beginning of stepped care implementation for psychological services to try and prevent services, to limit overburdening of services.

Cognitive assessments should be administered with a specific impairment in mind to identify either transient short-term impairments (such as delirium) or longer lasting deficits. Our search for mood disorders should also use simple screening assessments to attempt to distinguish between the wide ranges of problems. This would hopefully allow positive screens to be directed to psychological services, when appropriate, for a more detailed assessment for disorders that could impact on recovery.

For future research, this thesis demonstrates the need for either a global assessment across all patients in cognition/mood or assessments tailored to a patient's impairments. In order for data to be comparable across all patient cohorts and with prior research demonstrating the importance of processing speed in patients' recovery, I would suggest investigating and measuring processing speed for all patients regardless of impairments/severity of stroke. Furthermore, in order to assess specific domains in cognition, I think future research should concentrate on developing guidance, which allows health care staff to select an appropriate assessment for their patient.

Mood problems assessment is slightly more complex to generalise across stroke. Based on the research completed I would maintain a simple assessment for depression and anxiety at early stages (i.e. DISCS and an anxiety equivalent) then at

a later stage implement more detailed assessment for separation of symptoms and clear clinical problems affecting daily life.

However, despite these suggestions, these assessments will only become useful when we develop interventions that can help improve patient outcome. Therefore, research should also look into potential treatments that the patient/caregiver can easily practice/implement to improve mood and cognitive function.

Appendices

Appendix A - Email correspondence for ethical approval for usual practice questionnaire

Hi

Yes, if there is no patient identifiable data on the form, then Caldicott approval is not required.

Isobel

Isobel Brown

Information Governance Manager

Administration Building,

Western Infirmary

Dumbarton Road

Glasgow G11 6NT

From: Terence Quinn [mailto:Terry.Quinn@glasgow.ac.uk]

Sent: 15 November 2011 19:44

To: Brown, Isobel

Cc: Rosalind Lees; Broomfield, Niall

Subject: RE: advice / support with European audit

Dear Isobel

Thanks for help and advice with my recent EHS audit.

I have another quick information governance question.

My group has some funding from Chest Heart and Stroke Scotland to conduct a questionnaire audit of usual practice in mood and cognitive assessment in stroke units.

The questionnaire is voluntary, intended to be completed by senior staff and has no identifiable information other than hospital site.

I assume this would not require Caldicott Guardian approval - could you confirm?

Best wishes

Terry

Dr T J Quinn MD, MRCP, MBChB (hons), BSc MedSci (hons)

Lecturer in Geriatric Medicine

Cardiovascular and Medical Sciences, Walton Building

Glasgow Royal Infirmary, G4 0SF

Tel: +44 141 2114976

Fax +44 141 211 4033

Appendix B - Usual Practice Questionnaire

STROKE ASSESSMENT QUESTIONNAIRE

This 2 part questionnaire asks about what is involved in a general assessment of stroke survivors. Please tick the appropriate box(es) and/or fill in the blanks that apply to you and your stroke service. Thank you.

Staff group: NHS board/area your stroke service is in:

1. Cognitive Information:

Does your staff group (e.g. Drs, Nurses, OTs) assess patients' cognitive/mental function (e.g. memory and attention)?

Yes ☐ No ☐

Which test(s) are used? [tick all that apply]	Who administers the test(s)?		When after the stroke are they assessed with each test?		
	You	Other (please specify)	Acute admission	Rehabilitation	Outpatient clinic
Montreal Cognitive Assessment (MoCA)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cambridge Assessment Mental Disorders in the Elderly (CAMCOG)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abbreviated Mental Test (AMT)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Addenbrookes Cognitive Examination-Revised (ACE-R)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mini Mental State Examination (MMSE)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
National Institutes of Health Stroke Scale (NIHSS)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other/informal method (Please specify)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How does your approach to assessing cognitive/mental function (e.g. memory and attention) change in patients with speech/communication problems?

If cognitive problems are detected what is the next step(s)?

2. Mood Information:

Does your staff group (e.g. Drs, Nurses, OTs) assess patients' mood? Yes ☐ No ☐

Which test(s) are used? [tick all that apply]	Who administers the test(s)?		When after the stroke are they assessed with each test?		
	You	Other (please specify)	Acute admission	Rehabilitation	Outpatient clinic
Hospital Anxiety and Depression Scale (HADS)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Patient Health Questionnaire-9 (PHQ-9)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
General Health Questionnaire (GHQ)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Depression Intensity Scale Circles (DISCS)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Geriatric Depression Scale (GDS)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hamilton Depression Scale (HDS)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other/informal method (Please specify)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How does your approach change in patients with speech/communication problems?

If mood problems are detected what is the next step(s)?

Appendix C - Systematic review protocol

PROSPERO International prospective register of systematic reviews

Review title and timescale

- 1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Test accuracy of cognitive screening tests for diagnosis of post stroke dementia and cognitive impairment - systematic review and meta-analysis
- 2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
- 3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
14/03/2012
- 4 Anticipated completion date
Give the date by which the review is expected to be completed.
14/01/2014
- 5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ☒

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes
Risk of bias (quality) assessment	No	Yes
Data analysis	No	Yes

Provide any other relevant information about the stage of the review here.

Review team details

- 6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Rosalind Lees
- 7 Named contact email
Enter the electronic mail address of the named contact.
r.lees.1@research.gla.ac.uk
- 8 Named contact address
Enter the full postal address for the named contact.
Room 100, First Floor 44 Church Street Gardiner Institute Western Infirmary Institute of Cardiovascular and Medical Sciences University of Glasgow Glasgow G11 6NT
- 9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
0141 211 2542
- 10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
University of Glasgow

Website address:
<http://www.gla.ac.uk/>

- 11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Miss	Rosalind	Lees	Institute of Cardiovascular and medical Sciences, University of Glasgow
Dr	Johann	Selvarajah	Institute of neurological Sciences, Southern General Hospital
Dr	Candida	Fenton	MRC/CSO Social and Public Health Sciences Unit, University of Glasgow
Professor	Peter	Langhorne	Institute of Cardiovascular and Medical Sciences, University of Glasgow
Professor	David	Stott	Institute of Cardiovascular and Medical Sciences, University of Glasgow
Dr	Terence	Quinn	Institute of Cardiovascular and Medical Sciences, University of Glasgow

- 12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
This work and associated pilot work is supported by two research grants from Chest Heart and Stroke Scotland. As part of this work TQ spent time working with Cochrane Dementia and Cognitive Improvement Group and University of Birmingham, these study periods were supported by a Royal College of Physicians and Surgeons Glasgow travelling Fellowship and the Graham Wilson Travel Fund respectively. None of the funders have any direct input into the study or writing.
- 13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known
- 14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
-------	------------	-----------	----------------------

Review methods

- 15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
Test accuracy of multi-domain, direct to patient, cognitive screening tests for the diagnosis of dementia or cognitive impairment in a stroke-survivor population.

Test accuracy of brief, direct to patient, cognitive screening tests for the diagnosis of cognitive impairment using a more detailed, multi-domain assessment in a stroke-survivor population.

If data allows, our secondary objectives are to compare the effect of differing cutpoint scores used to define a threshold of "test positivity" and to compare the effects of heterogeneity with specific reference to setting and timing of assessment.

- 16 **Searches**
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will search multiple, cross-disciplinary electronic databases and resources specific to test accuracy and healthcare services research: ALOIS (Cochrane Dementia and Cognitive Improvement Group); ARIF (University of Birmingham); CINAHL (EBSCOhost); Embase (OvidSP); LILACS (Bireme); Medline (OvidSP); MEDION (Netherlands); Psychinfo (OvidSP) and the DARE, NHS EED, HTA databases (CRD). We will apply no language or date restrictions to the electronic searches. Translation services were used as necessary. "Grey" literature will be identified through hand searching of selected conference proceedings (European Stroke Conference; International Stroke Conference; UK Stroke Forum) and online searches of databases of theses or PhD abstracts. Handsearching of journals will be limited to recent publications (2010 onwards) in key journals Age and Ageing (British Geriatric Society); Cerebrovascular Diseases (European Stroke Organisation); Stroke (American Heart Association). We will not conduct more extensive handsearching as the specific benefits of this approach for dementia test accuracy is unproven. To complement our electronic and paper searching, we will contact research groups with a track record of test accuracy assessment research in stroke. Research teams working on reviews will be asked to share any papers with a potential stroke focus.
- 17 **URL to search strategy**
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.
http://www.crd.york.ac.uk/PROSPEROFILES/7432_STRATEGY_20140104.pdf

I give permission for this file to be made publicly available
No
- 18 **Condition or domain being studied**
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
post-stroke dementia
- 19 **Participants/population**
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Our focus is studies of stroke-survivors. Where the study population is a mix of stroke and other patient groups, we will include the study if the proportion of stroke-survivors was greater than 75%. We will make no distinction between ischaemic and haemorrhagic stroke but will exclude studies of traumatic intracerebral haemorrhage and studies exclusively concerned with subarachnoid haemorrhage. We will include studies conducted in any clinical setting and at any time period post stroke. We will operationalise stroke setting using the following descriptors: acute stroke unit (ASU); community; outpatient clinic (OPC); other inpatient hospital setting; rehabilitation unit and unspecified. We operationalised time since stroke as hyperacute (first 7 days); acute (8-14 days); post acute (15 days to 3 months); medium term (3 to 12 months); longer term (post 1 year) and unspecified. Where the population is mixed or details are not clear we will discuss and reach consensus on the most appropriate descriptor. We will not include case-studies (for the purpose of this review, we defined a case-study as having fewer than ten participants).
- 20 **Intervention(s), exposure(s)**
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Our index tests of interest are any direct to patient cognitive screening test, exemplars commonly employed in practice include Folstein's Mini-Mental State Examination (MMSE) and MoCA. We will not include informant based assessments or tests that require equipment or technology that we considered non-standard for a stroke service, for example virtual reality based assessments. Although we recognise that language and visuospatial function are important components of cognition, we will not include assessments of tools designed to exclusively test these domains, for example the Star Cancellation Test or the Boston Diagnostic Aphasia Examination. We will also not include those studies that compared one screening tool against another screening tool with no reference to a diagnostic gold standard. In addition to multi-domain screening tests, we are specifically interested in the accuracy of brief screening tests. We defined a brief screening test as any test that takes less than five minutes to complete. Our target condition of interest is all cause dementia or cognitive impairment. For our reference standard (gold standard) we will use clinical diagnosis of dementia or clinical diagnosis of any of the dementia subtypes. We will accept diagnosis made using any of the recognised classification systems, exemplars would be World Health Organisation International Classification of Disease (WHO-ICD) and the American Psychiatric Association Diagnostic and Statistical Manual (DSM). We will also accept a diagnosis of cognitive impairment when made using a detailed

neuropsychological testing battery. For assessment of test accuracy of brief screening tests we will accept results from a more detailed multi-domain screening assessment as our "diagnostic" reference standard. An example of a potentially eligible study would be a comparison of the brief Hodkinson's ten point abbreviated mental test (AMT) against a reference standard of MMSE.

- 21 **Comparator(s)/control**
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
n/a
- 22 **Types of study to be included initially**
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
We will include studies conducted in any clinical setting and at any time period post stroke. We will operationalise stroke setting using the following descriptors: acute stroke unit (ASU); community; outpatient clinic (OPC); other inpatient hospital setting; rehabilitation unit and unspecified. We operationalised time since stroke as hyperacute (first 7 days); acute (8-14 days); post acute (15 days to 3 months); medium term (3 to 12 months); longer term (post 1 year) and unspecified. Where the population is mixed or details are not clear we will discuss and reach a consensus on the most appropriate descriptor.
- 23 **Context**
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Search terms will be developed using a concepts based approach, employing Medical Subject Heading (MeSH) terms and other controlled vocabulary. Where possible we will use "explode" functions for keywords. Concepts of interest are "stroke", "dementia" and "cognitive assessment/screening". Within our "cognitive assessment" rubric we will include terms relating to those cognitive screening tests used in clinical practice and research based on our previous work in these fields. A full description of search terms will be included as online supplementary materials. We will supplement our sensitive search with a purposive search using a single database (Medline) and focuss on key cognitive screening tools of AMT, MMSE, MoCA and the Addenbrookes' Cognitive Examination Revised (ACE-R).
- 24 **Primary outcome(s)**
Give the most important outcomes.
We are principally interested in the accuracy of a screening test at a certain threshold score against a dichotomous variable "dementia/cognitive impairment" versus "no dementia/cognitive impairment". This will allow us to create standard "two by two" data tables describing binary test results cross-classified with binary reference standard

Give information on timing and effect measures, as appropriate.
- 25 **Secondary outcomes**
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
effect of differing cutpoint scores used to define a threshold of "test positivity" and comparing the effects of heterogeneity with specific reference to setting and timing of assessment.

Give information on timing and effect measures, as appropriate.
- 26 **Data extraction, (selection and coding)**
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
We will extract data to a study-specific pro-forma that collated clinical/demographic details of the participants, including timing and setting of assessment; details of the screening test and its administration and details of the reference standard and its application. We piloted the pro-forma against two of the included papers before use (pro-forma available from contact author). For screening tests that give an ordinal summary score, various cutpoints will be used to define "test positive" cases. Where data are given for a number of thresholds, we will extract separate data for each cutpoint. Where a study may have useable data but these were not presented in the published manuscript we will contact the authors directly. If the same data set was presented in more than one publication we will include the primary paper.
- 27 **Risk of bias (quality) assessment**
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and

whether and how this will influence the planned synthesis.

We will assess the quality of study reporting using the dementia specific extension to the Standards for Reporting of Diagnostic Accuracy (STARDdem) checklist. We will also tabulate STARDdem data for ease of review but will not create a summary score. We will assess methodological quality of each study using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2, www.bris.ac.uk/quadas/quadas-2). This tool incorporates domains specific to patient selection; index test; reference standard and patient flow. Each domain is assessed for risk of bias and the first three domains are also assessed for applicability. As part of a body of work around test accuracy, we had previously created QUADAS-2 "anchoring statements" specific to cognitive assessment. We will not calculate numerical QUADAS-2 summary scores, rather we will present a narrative summary with graphical description of risk of bias and applicability concerns. A quality concern specific to studies of stroke-survivors is around assessment of those with communication and so in addition to QUADAS-2 items we will assess for aphasia exclusion at study level.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

Where data allows we will use test accuracy functionality within RevMan 5.1 software to calculate sensitivity, specificity and corresponding 95% confidence intervals (95% CI) from our two by two data tables. The process will be performed separately for individual screening test at discrete threshold scores. We will create forest plots to allow a graphical display of the test accuracy of included studies and use visual inspection of these forest plots to assess for potential heterogeneity. Measures traditionally used to quantify heterogeneity, for example Higgins I², are not appropriate for test accuracy data synthesis.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

To create pooled summary measures, we will use additional software (Statistical Analysis Software, SAS v9.1, SAS Institute Inc, USA) to allow calculation of summary metrics using a bivariate approach. This method allows calculation of test accuracy summary estimates, accounting for the inherent inter-study variation at the level of: imprecision of sensitivity and specificity measures; variation beyond chance in sensitivity and any correlation that might exist between sensitivity and specificity. We will use a bespoke macro developed with assistance of a statistician with an interest in test accuracy studies (YT). Our summary metrics of interest will be pooled sensitivity and specificity and pooled positive and negative likelihood ratios. To describe pooled test accuracy we will create summary curves in receiver operating characteristic (ROC) space with corresponding 95% prediction intervals.

Review general information

30 Type of review

Select the type of review from the drop down list.

Diagnostic

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Scotland

33 Other registration details

List places where the systematic review title or protocol is registered (such as with the Campbell Collaboration, or The Joanna Briggs Institute). The name of the organisation and any unique identification number assigned to the review by that organization should be included.

Cochrane Library

- 34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.
- I give permission for this file to be made publicly available
Yes
- 35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Publication in a peer reviewed journal and dissemination of results at suitable conferences.
- Do you intend to publish the review on completion?
Yes
- 36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
dementia

screening

sensitivity

specificity

stroke
- 37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
- 38 Current review status
Review status should be updated when the review is completed and when it is published.
Completed but not published

31/03/2014
- 39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.
- 40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Appendix D Chapter 3 search strategy

Concept a) Stroke

1. Brain Ischemia.ti,ab (exploded)
2. Cerebrovascular*ti,ab (exploded)
3. Stroke.ti,ab (exploded)
4. or/1-3

Concept b) Cognitive disorders and tests

1. 3-stage commands.ti,ab
2. Abbreviated mental test.ti,ab
3. AMT.ti,ab
4. Addenbrooke's cognitive examination revised.ti,ab
5. ACE-R.ti,ab
6. Arizona battery for communication disorders of dementia.ti,ab
7. Assessment of motor and processing skills.ti,ab
8. AMPS.ti,ab
9. Block tapping.ti,ab
10. Brixton tests.ti,ab
11. California verbal learning test.ti,ab
12. CVLT.ti,ab
13. Cambridge cognitive examination revised.ti,ab
14. CAMCOG.ti,ab
15. Chessington occupational therapy Neurological assessment battery.ti,ab
16. COTNAB.ti,ab
17. Clock drawing.ti,ab
18. Cognitive linguistic quick tester.ti,ab
19. CLQT.ti,ab

20.Cognistat.ti,ab
21.Doors and people test.ti,ab
22.Galveston orientation and amnesia test.ti,ab
23.GOAT.ti,ab
24.Hayling test.ti,ab
25.Intersecting pentagons.ti,ab
26.Loewenstein occupational therapy cognitive assessment.ti,ab
27.LOTCA-G.ti,ab
28.Loethian aphasia stroke cognitive assessment.ti,ab
29.LASKA.ti,ab
30.Mental status questionnaire .ti,ab
31.MSQ.ti,ab
32.Mini mental state examination.ti,ab
33.MMSE.ti,ab
34.Montreal cognitive assessment.ti,ab
35.MoCA.ti,ab
36.Measure of cognitive linguistic ability.ti,ab
37.MCLA.ti,ab
38.OT cognitive screening tool.ti,ab
39.Perceive, recall, Plan and Perform.ti,ab
40.PRPP.ti,ab
41.Picture cards.ti,ab
42.Repeatable battery for the assessment of the neuropsychological status.ti,ab
43.RBANS.ti,ab
44.Rivermead behavioural memory test.ti,ab
45.RBMT.ti,ab
46.Rivermead perceptual assessment battery.ti,ab
47.RPAB.ti,ab

48.Screening Instrument for neuropsychological Impairments in Stroke.ti,ab

49.SINS.ti,ab

50.Short orientation memory and concentration test.ti,ab

51.SOMC.ti,ab

52.Verbal fluency test .ti,ab

53.Wessex head injury matrix.ti,ab

54.WHIM.ti,ab

55..Alzheimer Disease.ti.ab (exploded)

56..Cognition.ti.ab

57..Cognition Disorders.ti,ab (exploded)

58..Dementia.ti,ab (exploded)

59.Memory.ti,ab (exploded)

60.Vascular dementia.ti,ab

61. or/1-54

62. or/55-60

63. 61 or 62

Concept c) cognitive screening

1.Mass Screening.ti,ab (exploded)

2.Mental Status Schedule.ti,ab

3.Neuropsychological Tests.ti,ab (exploded)

4.Predictive Value of Teststi,ab

5.Psychiatric Status Rating Scales.ti,ab (exploded)

6.Psychological Tests.ti,ab

7.Reproducibility of Results.ti,ab

8.ROC Curve.ti,ab

9.Sensitivity.ti,ab (exploded)

10. Specificity.ti,ab (exploded)

11. Severity of Illness Index.ti,ab (exploded)

12. or/1-11

(Concept b OR concept c) AND concept a

Appendix E - STARDdem reporting guidance

(For studies with a dementia/cognitive impairment reference standard)

Section and Topic and item No.	STARD checklist item	Points of particular relevance to dementia
Title/Abstract/ Keywords		
1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity')	Studies reporting a sensitivity/specificity or 2x2 data derivable, fall within the scope of STARDdem and should be indexed accordingly.
Introduction		
2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	Some studies describing aims related to 'prognosis' or 'prediction' may also fall within the remit of STARDdem. Report test purpose: 'stand-alone' test or as an addition to other tests or clinical criteria.
Methods		
<i>Participants:</i>		

3	<p>The study population: The inclusion and exclusion criteria, setting and locations where data were collected</p> <p>See also Item 4 on recruitment and Item 5 on sampling</p>	<p>Key inclusion criteria: (a) demographic, especially age; (b) cognition- or disease-related criteria.</p> <p>Report referral pathways, precise locations of patient recruitment, where index test and reference standard were performed. For secondary/tertiary settings helpful to report the medical subspecialty or hospital dept (e.g. psychiatry, neurology).</p> <p>Diagnostic accuracy studies in dementia are often nested within larger cohort studies. If this is the case, then the targeted population for the cohort study and the method of cohort selection should be described and/or the parent study cited.</p>
4	<p>Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?</p> <p>See also Item 5 on sampling and Item 16 on participant loss at each stage of the study</p>	<p>For case-control design, report whether those in intermediate categories (e.g. possible AD or possible DLB) were excluded.</p>
5	<p>Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected</p> <p>See also Item 4 on recruitment and Item 16 on participant loss</p>	<p>Planned analyses showing how characteristics of the subgroup entering the study differ from the eligible population are strongly recommended (i.e. if a convenience sample has been used due to invasive nature of test/s).</p>

6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	Authors should report the timing of the analysis plan with respect to data collection: was the analysis plan set out in a protocol before index and reference standards were performed? If not, when was the analysis plan created?
<i>Test methods:</i>		
7	The reference standard and its rationale	For neuropathological and clinical reference standards the diagnostic criteria used should be specified. Where relevant, reference should be made to studies validating the criteria. Report if standard consensus clinical criteria incorporate the index test (incorporation rendering blinding of index test impossible).
8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard See also Item 10 concerning the person(s) executing the tests	<i>Use of scales:</i> specify details of administration, which version. <i>Clinical diagnostic criteria:</i> what information was available to inform the diagnoses; how the criteria were applied (e.g. by individual clinicians, by consensus conference, by semi-automated algorithm). <i>Imaging and laboratory tests:</i> specify materials and instruments, including sample handling and concordance with any harmonisation criteria. In new assays describe all steps in detail. Any particular preparation of participants should be described.
9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard	Explanation of any cut-off used is warranted; depending on clinical setting a more sensitive or more specific test is required.

10	<p>The number, training and expertise of the persons executing and reading the index tests and the reference standard</p> <p>See also Item 8</p>	<p>Especially where subjective judgments are involved, e.g. the interpretation of neuroimaging results.</p> <p>Report inter- and intra-rater agreement.</p> <p>Reference or describe the content of training materials used.</p> <p>Reference or describe details of lab certification and harmonised biomarker assays.</p>
11	<p>Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers</p> <p>See also Item 7</p>	<p>Also, the index test may form a part of the reference standard. This is often referred to as incorporation bias and renders blinding of the index test impossible.</p>
<i>Statistical methods:</i>		
12	<p>Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals)</p>	

13	Methods for calculating test reproducibility, if done	<p>Applies to the reference standard as well as to the index test. Both should be reported/adequately referenced. Recommend reporting inter-rater and test-retest reliability of reference standard as applied in the study being reported, rather than simply referring to other studies where reproducibility has been established.</p> <p>The training which image readers receive should be carefully described. Studies in which the accuracy of 'majority' judgements are reported should also report data for the minority judgements. Reports of the impact of training should clearly describe the population characteristics of the training group and whether it is representative of the group to which the test will be applied.</p>
Results		
<i>Participants:</i>		
14	When study was performed, including beginning and end dates of recruitment	<p>Pertinent particularly to longitudinal (delayed verification) studies, authors should report recruitment dates of the study (not to be confused with recruitment dates of the wider cohort study from which it might be drawn), and the beginning (first participant) and end (last participant) dates of the periods during which index test/s and reference standard were performed.</p> <p>Report the period for the index test and period for the reference standard separately if it is not clear.</p>

15	<p>Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms)</p> <p>See also Item 18</p>	<p>Report key demographic variables: age, sex and education.</p> <p>Report age distribution of sample in detail. Ethnicity and genetic factors (e.g. <i>APOE</i> genotype) may also be particularly important. The cognitive characteristics are covered in Item 18.</p>
16	<p>The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended)</p> <p>See also Item 3, Item 4 and Item 5</p>	
<i>Test results:</i>		
17	<p>Time-interval between the index tests and the reference standard, and any treatment administered in between</p>	<p>Specify the follow-up period for all subjects in relation to their outcomes. It should be specified whether or not participants had received any treatments which might affect disease progression.</p>
18	<p>Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition</p>	<p>Include a description of the severity of the target condition at the time the index test is performed. Usually captured by a cognitive score and/or duration of symptoms.</p> <p>For delayed verification studies report distribution of severity of disease and the degree of certainty (such as probable/possible) about the diagnosis at time of case ascertainment.</p> <p>Report other diagnoses (not target condition).</p>

19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard	
20	Any adverse events from performing the index tests or the reference standard	Report all adverse events, even if unlikely to be related to the diagnostic test performed.
<i>Estimates:</i>		
21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals) See also Item 12	
22	How indeterminate results, missing data and outliers of the index tests were handled	
23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done	
24	Estimates of test reproducibility, if done See also Item 13	
Discussion		

25	Discuss the clinical applicability of the study findings	<p>Key to clinical applicability are differences in age and comorbidity between the study population and the patients typically seen in clinical practice.</p> <p>Discuss issue of the 'added' or 'incremental' value of the index test if appropriate.</p> <p>Emphasise: 1. Stage of development of the test (e.g. proof of concept; defining accuracy in a typical spectrum of patients); 2. The further research needed to be done to make test applicable to population in whom likely to be applied in practice; 3. Whether sample was representative of the population in whom the test would be applied in practice.</p>
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Appendix F Methodology for developing dementia diagnosis QUADAS-2 anchoring

Anchoring statements to assist with assessment for risk of bias

Domain 1: Patient selection

Risk of bias: could the selection of patients have introduced bias? (high/low/unclear)

Was a consecutive or random sample of patients enrolled?: When sampling is used, the methods least likely to cause bias are consecutive sampling and random sampling, which should be stated and/or described. Nonrandom sampling or sampling based on volunteers is more likely to be at high risk of bias.

Weighting: High risk of bias

Was a case-control design avoided?: Case-control study designs have a high risk of bias, but sometimes they are the only studies available, especially if the index test is expensive and/or invasive. Nested case-control designs (systematically selected from a defined population cohort) are less prone to bias, but they will still narrow the spectrum of patients that receive the index test. Study designs (both cohort and case-control) that may also increase bias are those designs in which the study team deliberately increases or decreases the proportion of subjects with the target condition, for example, a population study may be enriched with extra dementia subjects from a secondary care setting.

Weighting: High risk of bias

Did the study avoid inappropriate exclusions?: The study will be automatically graded as unclear if exclusions are not detailed (pending contact with study authors). When exclusions are detailed, the study will be graded as 'low risk' if review authors feel that the exclusions are appropriate. Certain exclusions common to many studies of dementia are medical instability, terminal disease, alcohol/substance misuse, concomitant psychiatric diagnosis, and other neurodegenerative condition. However, if 'difficult to diagnose' groups are excluded, this may introduce bias, so exclusion criteria must be justified. For a community

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 August 28.

sample, we would expect relatively few exclusions. Post hoc exclusions will be labelled 'high risk' of bias.

Weighting: High risk of bias

Applicability: are there concerns that the included patients do not match the review question? (high/low/unclear)—The included patients should match the intended population as described in the review question. If not already specified in the review inclusion criteria, the setting will be particularly important - the review authors should consider population in terms of symptoms, pretesting, and potential disease prevalence. Studies that use very selected subjects or subgroups will be classified as low applicability, unless they are intended to represent a defined target population, for example, people with memory problems referred to a specialist and investigated by lumbar puncture.

Domain 2: Index test

Risk of bias: could the conduct or interpretation of the index test have introduced bias? (high/low/unclear)

Were the index test results interpreted without knowledge of the reference standard?: Terms such as 'blinded' or 'independently and without knowledge of' are sufficient, and full details of the blinding procedure are not required. This item may be scored as 'low risk' if it is explicitly described, or if there is a clear temporal pattern to the order of testing that precludes the need for formal blinding (e.g. all [neuropsychological test] assessments were performed before the dementia assessment). As most neuropsychological tests are administered by a third party, knowledge of dementia diagnosis may influence their ratings; tests that are self-administered, for example, by using a computerised version, may have less risk of bias.

Weighting: High risk

Were the index test thresholds pre-specified?: For neuropsychological scales, there is usually a threshold above which subjects are classified as 'test positive'; this may be referred to as threshold, clinical cut-off, or dichotomisation point. Different thresholds are used in different populations. A study is classified at higher risk of bias if the authors define the optimal cut-off post hoc based on their own study data. Certain papers may use an alternative methodology for analysis that does not use thresholds, and these papers should be classified as not applicable.

Weighting: Low risk

Were sufficient data on (neuropsychological test) application given for the test to be repeated in an independent study?: Particular points of interest include method of administration (e.g. self-completed questionnaire versus direct questioning interview), nature of informant, and language of assessment. If a novel form of the index test is used, for example, a translated questionnaire, details of the scale should be included and a reference given to an appropriate descriptive text, and evidence of validation should be provided.

Weighting: Low risk

Applicability: are there concerns that the index test, its conduct, or its interpretation may differ from the review question? (high/low/unclear)—

Variations in the length, structure, language, and/or administration of the index test may all affect applicability if they differ from those specified in the review question.

Domain 3: Reference standard

Risk of bias: could the reference standard, its conduct, or its interpretation have introduced bias? (high/low/unclear)

Is the reference standard likely to correctly classify the target condition?: Commonly used international criteria that can assist with clinical diagnosis of dementia include those detailed in DSM-IV and ICD-10. Criteria specific to dementia subtypes include but are not limited to NINCDS-ADRDA criteria for Alzheimer's dementia; McKeith criteria for Lewy body dementia; Lund criteria for frontotemporal dementia; and NINDS-AIREN criteria for vascular dementia. When the criteria used for assessment are not familiar to the review authors and the Cochrane Dementia and Cognitive Improvement Group, this item should be classified as 'high risk of bias.'

Weighting: High risk

Were the reference standard results interpreted without knowledge of the results of the index test?: Terms such as 'blinded' or 'independent' are sufficient, and full details of the blinding procedure are not required. This may be scored as 'low risk' if explicitly described, or if a clear temporal pattern to the order of testing is evident (e.g. all dementia assessments performed before (neuropsychological test) testing).

Informant rating scales and direct cognitive tests present certain problems. It is accepted that informant interview and cognitive testing are usual components of clinical assessment for dementia; however, specific use of the scale under review in the clinical dementia assessment should be scored as high risk of bias.

Weighting: High risk

Was sufficient information on the method of dementia assessment given for the assessment to be repeated in an independent study?: Particular points of interest for dementia assessment include the training/expertise of the assessor, whether additional information (e.g. neuroimaging; other neuropsychological test results) was available to inform the diagnosis, and whether this was available for all participants.

Weighting: Variable risk, but high risk if method of dementia assessment not described

Applicability: are there concerns that the target condition as defined by the reference standard does not match the review question? (high/low/unclear)—

There is the possibility that some methods of dementia assessment, although valid, may

diagnose a smaller or larger proportion of subjects with disease than in usual clinical practice. In these instances, the item should be rated 'poor applicability.'

Domain 4: Patient flow and timing (N.B. refer to, or construct, a flow diagram)

Risk of bias: could the patient flow have introduced bias? (high/low/unclear)

Was there an appropriate interval between the index test and the reference standard?:

For a cross-sectional study design, there is potential for the subject to change between assessments; however, dementia is a slowly progressive disease that is not reversible. The ideal scenario would be a same-day assessment, but longer periods of time (e.g. several weeks or months) are unlikely to lead to a high risk of bias. For delayed-verification studies, the index and reference tests are necessarily separated in time, given the nature of the condition.

Weighting: Low risk

Did all subjects receive the same reference standard?: In some scenarios, subjects who score 'test positive' on the index test have a more detailed assessment for the target condition. When dementia assessment (or the reference standard) differs between subjects, this should be classified as high risk of bias.

Weighting: High risk

Were all subjects included in the final analysis?: Attrition will vary with study design. Delayed-verification studies will have higher attrition than cross-sectional studies because of mortality, and this is likely to be greater in subjects with the target condition. Dropouts (and missing data) should be accounted for. Attrition that is higher than expected (compared with other similar studies) should be treated as a high risk of bias. We have defined a cut-off of greater than 20% attrition as being high risk, but this will be highly dependent on the length of follow-up in individual studies.

Weighting: High risk

Appendix G Local ethics committee approval - Chapter 5

WoSRES

West of Scotland Research Ethics Service



Ms Rosalind Lees
Institute of Cardiovascular and Medical Sciences
School of Medicine
University of Glasgow
The Gardiner Institute
Western Infirmary
Dumbarton Road
Glasgow G11 6NT

West of Scotland REC 1
Ground Floor, Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT

Date 26th November 2012
Direct 0141-211-6270
line
Fax 0141-211-1847

Dear Ms Lees

Study title: Feasibility and diagnostic test accuracy of early mood screening in the delayed diagnosis of clinically important mood disorders: Comparison of Hospital Anxiety and Depression Scale and Depression Intensity Scale Circles in stroke survivors.

REC reference: 12/WS/0275

Thank you for your letter of 21st November 2012. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 09 November 2012

Documents received

The documents received were as follows:

Document	Version	Date
Covering Letter		21 November 2012
GP/Consultant Information Sheets		
Other: Flow chart	1	13 November 2012
Other: Data extraction sheet	1.1	15 August 2012
Other: GP Letter 1	1.1	09 August 2012
Other: GP Letter 2	1.1	
Participant Consent Form	1.1	13 November 2012
Participant Information Sheet	1.1	13 November 2012
Protocol	1.1	09 August 2012

Approved documents

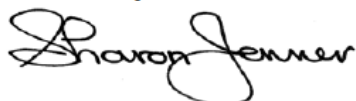
The final list of approved documentation for the study is therefore as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		21 November 2012
Investigator CV	N Broomfield	
Investigator CV	T Quinn	14 February 2012
Investigator CV	R Lees	13 September 2012
Other: References	1	09 August 2012
Other: Flow chart	1	13 November 2012
Other: GP Letter 1	1.1	09 August 2012
Other: GP Letter 2	1.1	
Participant Consent Form	1.1	13 November 2012
Participant Information Sheet	1.1	13 November 2012
Protocol	1.1	09 August 2012
Questionnaire: HADS	1	09 August 2012
Questionnaire: Cognitive Assessment Card (IQCODE)	1	09 August 2012
Questionnaire: DISCs (Depression Intensity Scale Circles)		09 August 2012
Questionnaire: M.I.N.I.		09 August 2012
Questionnaire: Confusion Assessment Method (CAM5)		
Questionnaire: Oxfordshire Community Stroke Project Classification (OCSP)		
Questionnaire: NIH Stroke Scale		
REC application	1	08 October 2012

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

12/WS/0275	Please quote this number on all correspondence
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Yours sincerely



Miss Sharon Jenner
Assistant Committee Co-ordinator

E-mail: sharon.jenner@ggc.scot.nhs.uk

Copy to: *Dr Niall Broomfield,*
Dr Erica Packard, NHS Greater Glasgow and Clyde

Appendix H - Caldicott Guardian approval: audit data collection - Chapter 5



Application for Caldicott Guardian approval for use of patient identifiable data (PID)

Audit / Project Title

Audit of secondary prevention following stroke in Glasgow
Forms part of European Society Hypertension audit of stroke secondary prevention

Details of individual / organisation requesting data

Internal: Dr Terry Quinn (Specialist Trainee Medicine, NHS GG&C)
Prof Matthew R Walters (Professor of Pharmacology and Stroke and Honorary
Consultant, Western Infirmary Glasgow)
External: European Society Hypertension

Purpose for which data are to be used

Audit of clinical practice locally and across Europe. Specifically, audit of adherence to European guidelines on pharmacological stroke secondary prevention measures.

Which identifiable data items are required?

Forename ☐ Surname ☐ DoB ☐ Age x Sex x Address ☐
Post code ☐ Clinical Information ☐ Other ☐ (please provide further details below)

Please justify why each identifiable data item is required

Age and sex are required for this audit as a primary aim of the audit is to examine for any potential difference in process of care based on age or sex.

Who will have access to this information?

Internal:

Dr Terry Quinn (Specialist Trainee Medicine, NHS GG&C)

Prof Matthew R Walters (Professor of Pharmacology and Stroke and Honorary Consultant, Western Infirmary Glasgow)

External: European Society Hypertension - information from each site will be managed by a single data-manger using an online password protected secure web portal

Storage and use of personal data during the audit/project

Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)

- x Access to medical records
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal identifiable data on any of the following:
 - ☐ Manual files, including x-rays
 - ☐ NHS Computers
 - ☐ Home or other personal computers
 - ☐ University computer
 - ☐ Private company computer
 - ☐ Laptop computers

Additional Information:

Please list your organisation's Data Protection Registration Number
(if external to NHSGGC)

NHSGG&C

Person responsible for the requested data

Name Dr Terry Quinn.....

Job Title Specialist Trainee, Glasgow Royal Infirmary.....

Signature: **Date:**24/10/11.....

Note:

- Please provide copies of any other relevant supporting documentation (e.g. ethics approval, patient information leaflet etc.)
- Appendix A details the Caldicott Principles

The release of data as described above is: **approved / not approved**

Caldicott Guardian **Date:**.....

Caldicott principles

Principle 1 - Justify the purpose(s)

Every proposed use or transfer of patient-identifiable information within or from an organisation should be clearly defined and scrutinised, with continuing uses regularly reviewed, by an appropriate guardian.

Principle 2 - Don't use patient-identifiable information unless it is absolutely necessary

Patient-identifiable information items should not be used unless there is no alternative.

Principle 3 - Use the minimum necessary patient-identifiable information

Where use of patient-identifiable information is considered to be essential, each individual item of information should be justified with the aim of reducing identifiability.

Principle 4 - Access to patient-identifiable information should be on a strict need-to-know basis

Only those individuals who need access to patient-identifiable information should have access to it, and they should only have access to the information items that they need to see.

Principle 5 - Everyone should be aware of their responsibilities

Action should be taken to ensure that those handling patient-identifiable information - both clinical and non-clinical staff - are made fully aware of their responsibilities and obligations to respect patient confidentiality.

Principle 6 - Understand and comply with the law

Every use of patient-identifiable information must be lawful. Someone in each organisation should be responsible for ensuring that the organisation complies with legal requirements.

Caldicott Guardian for NHS Greater Glasgow & Clyde

Richard Copland
Director of Health, Information & Technology
Greater Glasgow & Clyde NHS Board
J B Russell House
Gartnavel Royal Hospital
Gt. Western Road
Glasgow

All queries in the first instance should be made to:

Isobel Brown, Information Governance Manager
Tel: 0141 211 1790 or E-Mail: Isobel.brown@ggc.scot.nhs.uk

Appendix I - Email correspondence for use of audit data for another project - Chapter 5

Thanks for getting back to me. I have approved this project on behalf of the Caldicott Guardian. If you require a copy of the signed CG form, please let me know the best address for sending this.

Isobel

Isobel Brown
Information Governance Manager
Administration Building,
Western Infirmary
Dumbarton Road
Glasgow G11 6NT
0141 211 (5) 1790

From: Terence Quinn [<mailto:Terry.Quinn@glasgow.ac.uk>]
Sent: 14 November 2011 17:05
To: Brown, Isobel
Subject: RE: advice / support with European audit

Dear Isobel

Thanks, age and sex are only directly patient identifiable demographics that will be shared with EHS. Dr Roberts is aware of the project.

best wishes

Terry

Dr T J Quinn MD, MRCP, MBChB (hons), BSc MedSci (hons)
Lecturer in Geriatric Medicine

Cardiovascular and Medical Sciences, Walton Building
Glasgow Royal Infirmary, G4 0SF
Tel: +44 141 2114976
Fax +44 141 211 4033

From: Brown, Isobel [Isobel.Brown@ggc.scot.nhs.uk]
Sent: 14 November 2011 16:23
To: Terence Quinn
Subject: RE: advice / support with European audit

Hi

Can I check with you that only the age and sex of the patients will be shared with EHS along with clinical data and that this audit has the approval and support of Dr Roberts?

Thanks

Isobel

Isobel Brown

Appendix J - National ethics committee approval - Chapter 6 rehabilitation study

Scotland A Research Ethics Committee

Dr Terence Quinn
Lecturer in Geriatric Medicine
University of Glasgow
Cardiovascular and Medical Sciences
Walton Building
Glasgow Royal Infirmary
Glasgow
G4 0SF

Research Ethics Service
2nd Floor Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone: 0131 465 5680
Fax: 0131 465 5789
www.nres.nhs.uk



Date: 3 April 2014
Your Ref.:
Our Ref.: 14/SS/0042
Enquiries to: Walter Hunter
Extension: 35680
Direct Line: 0131 465 5680
Email: walter.hunter@nhslothian.scot.nhs.uk

Dear Dr Quinn

Study title: Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-iii), Montreal Cognitive Assessment and Mini mental State examination (MMSE).
REC reference: 14/SS/0042
IRAS project ID: 118955

I refer to Miss Lees' e-mail dated 3 April 2014.. I can confirm the Scotland A REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 3 April 2014

Documents received

The documents received were as follows:

Document	Version	Date
Participant Consent Form: Patient preferred carer/friend/relative	3	03 April 2014
Participant Consent Form: Legal representative	3	03 April 2014
Participant Information Sheet: Patient preferred carer/friend/relative	3	03 April 2014
Participant Information Sheet: Legal representative	3	02 April 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
REC application: IRAS Form	3.5	19 February 2014

Chairman Dr Ian Zealley
Vice-Chairman Dr Colin Selby

Protocol	1	18 November 2013
Investigator CV: Dr Quinn		
Investigator CV: Professor Stott		
Investigator CV: Dr Broomfield		
Investigator CV: Miss Lees		
Investigator CV: Ms Hendry		
Participant Information Sheet: Participant	2	01 April 2014
Participant Consent Form: Participant	2	01 April 2014
Participant Information Sheet: Welfare Guardian/Nearest Relative	3	02 April 2014
Participant Consent Form: Welfare Guardian/Nearest Relative	3	02 April 2014
Participant Information Sheet: Carer/Friend/Relative	3	03 April 2014
Participant Consent Form: Carer/Friend/Relative	3	03 April 2014
Flowchart	1	18 November 2013
Questionnaire: MMSE		
Questionnaire: CQUIN SQ Scoring Sheet		
Questionnaire: MoCA Scoring Sheet		
Questionnaire: NIHSS Scoring Sheet		
Questionnaire: Yale SQ Scoring Sheet		
Questionnaire: ACE-III		
Questionnaire: PHQ-9		
Questionnaire: IQ CODE		
Response to request for further information		02 April 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

REC reference number: 14/SS/0042-Please quote this number on all correspondence

Yours sincerely



WALTER HUNTER
REC Manager

Appendix K - Patient Information sheet and consent form - Chapter 6

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
Glasgow G11 6NT
0141 211 2542



Contact information

If you wish any further information about the study please contact Dr Terence J Quinn; terry.quinn@glasgow.ac.uk, 0141-211-4976, Dr Niall Broomfield; niall.broomfield@ggc.scot.nhs.uk, 0141-211-4976 or Miss Rosalind Lees; r.lees.1@research.gla.ac.uk, 0141-211-2542

Information sheet for patients in clinical research project

Title of project

Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-III), Montreal Cognitive Assessment (MoCA) and Mini mental State examination (MMSE).

You are being invited to take part in a clinical research study of the ability of paper and pencil tests to accurately assess thinking skills after stroke.

Before you make a decision, it is important that you fully understand why the research is being done and what will be involved. This study is part of a PhD study involving patients with stroke.

Please take time to read the following information carefully. Feel free to ask us any questions or to provide more information if anything is unclear before making a decision.

Thank you.

Purpose of study

You have been diagnosed as having had a stroke. After a stroke many people develop changes in their memory, concentration and thinking skills. Guidelines recommend we assess memory and thinking after a stroke, but we are not sure of the best way to do this.

This study is looking at three paper and pencil based tests of thinking. We wish to see if these tests can be used after a stroke and which test best gives the most useful information. This is important as early detection of memory and thinking problems may allow treatment of these problems.

Why have I been chosen?

All patients that have been diagnosed with a stroke will be considered for participation. We will be recruiting over 5 months.

Version 2, 01/04/2014

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form.

You are free to withdraw at any time and do not have to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

The researchers are not involved with your general care and will not be involved with treatment of any thinking problems. The results of the tests will be shared with the stroke team looking after you.

What do I have to do?

You will be given three different thinking and memory tests to complete. They will be a combination of written, picture and verbal format. Specific instructions will be given as the tests are administered. We will also ask you some questions about your mood and feelings. In total this will take approximately 45-50 minutes. We will break things into two sessions of around 25 minutes. The tests will be administered by one of the two researchers.

A multiple choice questionnaire asking about your memory and thinking skills before the stroke will also be given to someone who sees you on a regular basis i.e. family member or friend. This will take 5-10 minutes to complete.

What are the possible benefits to taking part?

There are no direct benefits to you of taking part in this study. However by taking part you will help us decide on the best way to test thinking and memory after stroke. We hope that this study will improve our management of patients with stroke in the future.

What if something goes wrong?

If any problems are encountered during assessment that cannot be resolved for example you suddenly become unwell, assessment will be ended and where necessary a member of the treating clinical team will be notified. You have the right to withdraw from assessment at anytime without providing a reason and with no impact to the standard of care received. If you are unhappy about any aspect of the study and wish to make a formal complaint, please contact the researcher in the first instance but the normal NHS complaints mechanism is also available to you.

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
Glasgow G11 6NT
0141 211 2542



What will happen to the results of the study?

The results of your tests will be shared with the clinical team working within the rehabilitation unit. We hope to publish the final results of the study in a scientific journal and discuss the study at stroke professional meetings. Your personal details will not be available in any of these materials. If you are interested in the results when the study is complete, details can be posted to you.

Confidentiality

Your scores on the thinking tests will be shared with hospital team. All personal information collected by the research team will be anonymised and stored in a secure way.

Part of our questions on current feelings includes asking about depression and suicide. If we suspect severe depression or suicidal thoughts, questioning will be stopped and your physician contacted immediately. You may also be referred to appropriate specialised help.

Who is organising and funding the study?

This study is being organised by the Institute of Cardiovascular and Medical Sciences and the Department of Clinical Psychology in the Western Infirmary. The researchers will receive no remuneration for including you in the study.

Who has reviewed this study?

This study has been reviewed and approved by the Scotland A REC.

SUMMARY

If you agree to participate you will be asked to complete some tests assessing your thinking skills and mood.

Name of Researchers

Miss Rosalind Lees and Kirsty Hendry, PhD postgraduate students, University of Glasgow.
Dr Terry Quinn, Lecturer in Geriatric Medicine, University of Glasgow.
Dr Niall Broomfield, Honorary Clinical Senior Lecturer, Institutes of Cardiovascular and Medical Sciences/Health and Wellbeing, University of Glasgow.

Name of sponsors

NHS Greater Glasgow and Clyde

Version 2, 01/04/2014

Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-III), Montreal Cognitive Assessment (MoCA) and Mini mental State examination (MMSE).

PATIENT CONSENT FORM

Study number:

Subject Number:

Please read the information below, sign and date if in agreement

Please initial the BOX

1. I confirm that I have read and understood the information sheet version 2 dated 01/04/14 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or rights being affected. ☐
3. I understand that sections of my medical notes may be looked at by the investigators named above and/or by the sponsor if relevant. I give permission for these individuals to have access to my records. ☐
4. I understand that results will be used for research purposes and shared with the clinical team. ☐
5. I understand that in the event that suicidal thoughts or concerns regarding severe depression are disclosed to the researcher then the clinical team will be immediately informed regardless of my preference. ☐
6. I agree to take part in the above study. ☐

Name of Patient

Date

Signature

Name of person taking consent

Date

Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patient's notes

Version 2, 01/04/2014

Appendix L - Preferred carer/friend information sheet and consent form - Chapter 6

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
Glasgow G11 6NT
0141 211 2542



Contact information

If you wish any further information about the study please contact Dr Terence J Quinn; terry.quinn@glasgow.ac.uk, 0141-211-4976, Dr Niall Broomfield; niall.broomfield@ggc.scot.nhs.uk, 0141-211-4976 or Miss Rosalind Lees; r.lees.1@research.gla.ac.uk, 0141-211-2542

Patient's preferred carer/friend/relative information sheet for clinical research project

Title of project

Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-III), Montreal Cognitive Assessment (MoCA) and Mini mental State examination (MMSE).

You are being invited to take part in a clinical research study of the ability of paper and pencil tests to accurately assess thinking skills after stroke. You will be asked to provide information of your family member/friend's thinking ability and memory **BEFORE** they had a stroke.

Before you make a decision, it is important that you fully understand why the research is being done and what will be involved. This study is part of a PhD in cognitive and mood assessment of stroke survivors. The students involved are Miss Rosalind Lees and Miss Kirsty Hendry.

Please take time to read the following information carefully. Feel free to ask us any questions or to provide more information if anything is unclear before making a decision.

Thank you.

Purpose of study

After a stroke many people develop changes in their memory, concentration and thinking skills. You have been nominated by one of the patients in this rehab ward as someone who could comment on their memory and thinking.

This study is looking at paper and pencil based tests of thinking. We wish to see if these tests can be used to detect thinking problems in patients who have had a stroke. This is important as early detection of memory and thinking problems may allow treatment of these problems.

Version 3, 03/04/2014

Why have I been chosen?

A patient in the stroke rehabilitation unit has identified you as someone who can comment on their memory and thinking.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form.

You are free to withdraw at any time and do not have to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care the patient will receive.

The researchers are not involved with your family member's general care and will not be involved with treatment of any thinking problems. The results of the tests will be shared with the team looking after your family member/friend.

What do I have to do?

You will be given two different questionnaires to complete. The first consists of a single question judging thinking abilities over the past year **BEFORE** the stroke with a 'yes' or 'no' answer. The second test is a multiple choice questionnaire that has a list of 16 everyday tasks that we will ask for you to rate how your family member has managed these over the past 10 years **BEFORE** the stroke. These will take around 5 minutes to complete.

What are the possible benefits to taking part?

There are no direct benefits to you or your family member for taking part in this study. However by taking part you will help us decide on the best way to test for thinking and memory problems after stroke. We hope that this study will improve our management of those with stroke.

What if something goes wrong?

You have the right to withdraw from assessment at anytime without providing a reason and with no impact to the care received by your family member/friend. If you are unhappy about any aspect of the study and wish to make a formal complaint, please contact the researcher in the first instance but the normal NHS complaints mechanism is also available to you.

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
Glasgow G11 6NT
0141 211 2542



What will happen to the results of the study?

The results of your tests will be shared with the clinical team working within the rehabilitation unit. We hope to publish the final results of the study in a scientific journal and discuss the study at stroke professional meetings. Your personal details will not be available in any of these materials. If you are interested in the results when the study is complete, details can be posted to you.

Confidentiality

Scores on the questionnaires will be shared with hospital rehabilitation team. All information collected by the research team will be anonymised and stored in a secure way.

Who is organising and funding the study?

This study is being organised by the Institute of Cardiovascular and Medical Sciences and the Department of Clinical Psychology in the Western Infirmary. The researchers will receive no remuneration for including you in the study.

Who has reviewed this study?

This study has been reviewed and approved by Scotland A REC.

SUMMARY

If you agree to participate you will be asked to complete some tests assessing your family member/friend's memory and thinking skills **BEFORE** they had a stroke.

Name of Researchers

Miss Rosalind Lees, Miss Kirsty Hendry PhD postgraduate students, University of Glasgow.

Dr Terry Quinn, Lecturer in Geriatric Medicine, University of Glasgow.

Dr Niall Broomfield, Honorary Clinical Senior Lecturer, Institutes of Cardiovascular and Medical Sciences/Health and Wellbeing, University of Glasgow.

Name of sponsor

NHS Greater Glasgow and Clyde

Version 3, 03/04/2014

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
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0141 211 2542



Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-III), Montreal Cognitive Assessment (MoCA) and Mini mental State examination (MMSE).

CONSENT FORM FOR PATIENT'S PREFERRED CARER/FRIEND/RELATIVE

Study number:

Subject Number (Participant):

Please read the information below, sign and date if in agreement

Please initial the BOX

1. I confirm that I have read and understood the information sheet version 3 dated 03/04/14 for the above study and have had the opportunity to ask questions.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my family member/friend's medical care or rights being affected.

☐

3. I understand that results will be used for research purposes and shared with the clinical team.

☐

4. I agree to take part in the above study.

☐

Name of carer/friend/relative

Date

Signature

Name of person taking consent

Date

Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patient's notes

Version 3, 03/04/2014

Appendix M - Legal representative information sheet and consent form - Chapter 6

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
Glasgow G11 6NT
0141 211 2542



Contact information

If you wish any further information about the study please contact Dr Terence J Quinn; terry.quinn@glasgow.ac.uk, 0141-211-4976, Dr Niall Broomfield; niall.broomfield@ggc.scot.nhs.uk, 0141-211-4976 or Miss Rosalind Lees; r.lees.1@research.gla.ac.uk, 0141-211-2542

Information sheet for legal representative (welfare guardian/nearest relative) providing consent for patients lacking capacity to consent in clinical research project

Title of project

Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-III), Montreal Cognitive Assessment (MoCA) and Mini mental State examination (MMSE).

You are being invited to provide consent for your family member/friend to take part in a clinical research study of the ability of paper and pencil tests to accurately assess thinking skills after stroke.

Before you make a decision, it is important that you fully understand why the research is being done and what will be involved. This study is part of a PhD involving stroke patients.

Please take time to read the following information carefully. Feel free to ask us any questions or to provide more information if anything is unclear before making a decision.

Thank you.

Purpose of study

Your family member/friend has been diagnosed as having had a stroke. After a stroke many people develop changes in memory, concentration and thinking skills. Guidelines recommend that thinking and memory skills are assessed after a stroke, but we are not sure of the best way to perform this.

This study is looking at paper and pencil based tests of thinking. We wish to see if these tests can be used to detect thinking problems in patients who have had a stroke. This is important as early detection of memory and thinking problems may allow treatment of these problems.

Why has my family member/friend been chosen?

All patients that have been diagnosed with a stroke will be considered for participation. We will be recruiting over 5 months.

Version 3, 02/04/2014

Do they have to take part?

No. It is up to you to decide whether or not your family member/friend takes part. You are free to withdraw consent at any time and do not have to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your family member will receive.

The researchers are not involved with general care and will not be involved with treatment of any thinking problems. The results of the tests will be shared with the clinical team.

What will happen to my family member/friend if I provide consent?

The assessments will be completed while they are still in hospital. No extra trips to the hospital will be required. The results will be shared with the team looking after your family member on the ward.

Your family member/friend will be given three different thinking and memory tests to complete. They will be a combination of written, picture and verbal format. Specific instructions to tasks will be given as the tests are administered. We will also ask them some questions about their mood and feelings. In total this will take approximately 45-50 minutes. We will break things into two sessions of around 25 minutes. The tests will be administered by one of the two researchers.

What do I have to do?

If you agree for your family member/friend to participate you will be asked to sign a consent form on behalf of your family member/friend. A multiple choice questionnaire asking about memory and thinking before the stroke will be provided to you or someone else who knows the patient well. This will take 5-10 minutes to complete.

What are the possible benefits to my family member/friend taking part?

There are no direct benefits to your family member/friend of taking part in this study. However by taking part they will help us decide on the best way to test for thinking and memory problems after stroke. We hope that this study will improve our management of patients with stroke.

What if something goes wrong?

If any problems are encountered during assessment that cannot be resolved for example the patient suddenly become unwell, assessment will be ended and where necessary a member of the clinical team will be notified. If you are unhappy about any aspect of the study and wish to make a formal complaint, please contact the researcher in the first instance but the normal NHS complaints mechanism is also available to you.

Institute of Cardiovascular and Medical Sciences,
University of Glasgow
The Gardiner Institute, Western Infirmary
Glasgow G11 6NT
0141 211 2542



What will happen to the results of the study?

The results of your tests will be shared with the clinical team working within the rehabilitation unit. We hope to publish the final results of the study in a scientific journal and discuss the study at stroke professional meetings. Personal details will not be available in any of these materials. If you are interested in the results when the study is complete, details can be posted to you.

Confidentiality

Scores on the thinking tests will be shared with hospital rehabilitation team. All personal information collected by the research team will be anonymised and stored in a secure way.

Part of our questions on mood includes asking about depression and suicide. If we suspect severe depression or suicidal thoughts, questioning will be stopped and the treating physician contacted immediately. The patient may also be referred to appropriate specialised help.

Who is organising and funding the study?

This study is being organised by the Institute of Cardiovascular and Medical Sciences and the Department of Clinical Psychology in the Western Infirmary. The researchers will receive no remuneration for including you in the study.

Who has reviewed this study?

This study has been reviewed and approved by the Scottish A Research Ethics Committee.

SUMMARY

If you agree to provide consent for your family member to participate they will be asked to complete some tests assessing thinking skills and mood.

Name of Researchers

Miss Rosalind Lees, Miss Kirsty Hendry PhD postgraduate students, University of Glasgow.

Dr Terry Quinn, Lecturer in Geriatric Medicine, University of Glasgow.

Dr Niall Broomfield, Honorary Clinical Senior Lecturer, Institutes of Cardiovascular and Medical Sciences/Health and Wellbeing, University of Glasgow.

Name of sponsors

NHS Greater Glasgow and Clyde

Version 3, 02/04/2014

Feasibility and comparative test properties of three direct cognitive assessment tools in a stroke rehabilitation setting: Comparison of the Addenbrooke's cognitive examination- third edition (ACE-iii), Montreal Cognitive Assessment and Mini mental State examination (MMSE).

LEGAL REPRESENTATIVE CONSENT FORM

Study number:

Subject Number:

Please read the information below, sign and date if in agreement

Please initial the BOX

1. I confirm that I have read and understood the information sheet version 3 dated 02/04/14 for the above study and have had the opportunity to ask questions. ☐
2. I understand that consent is voluntary and that I am free to withdraw it at any time without giving any reason and without medical care or rights being affected. ☐
3. I understand that sections of my family member/friend's medical notes may be looked at by the investigators named above and/ or by the sponsor where it is relevant. I give permission for these individuals to have access to my family member/friend's records. ☐
4. I understand that results will be used for research purposes and shared with the clinical team. ☐
5. I understand that in the event that suicidal thoughts or concerns regarding severe depression are disclosed to the researcher then the clinical team will be immediately informed regardless of patient preference. ☐
6. I agree to my relative taking part in the above study. I confirm that i am the nearest relative for _____ and that no other nearest relative or welfare attorney or guardian exists. ☐

Relationship to patient _____

I confirm that I am the welfare Attorney or Guardian for _____

_____	_____	_____
Name of person giving consent	Date	Signature

_____	_____	_____
Name of person taking consent	Date	Signature

(If different from the researcher)

1 copy to the patient, 1 copy to the researcher, 1 Original for the patient's notes

Version 3, 02/04/2014

Appendix N - Opinion article

Stroke cognitive screening: The good, the bad and the unknown

This opinion article was commissioned by the editors of the journal International Journal of Therapy and Rehabilitation, in response to an original research article on cognitive assessments in stroke settings. In the context of rising publicity surrounding dementia assessment and polarised opinion on the utility of cognitive screening for impairments, this article was written to point out the issues and potential benefits of cognitive screening as well as what is missing from research. With multi-domain cognitive impairment and dementia prevalent in stroke survivors and a push for screening in guidelines despite few interventions available, this article attempts to help clarify our current understanding of the role of cognitive screening in stroke.

Post-stroke cognitive screening: The good, the bad and the unknown

Cognitive impairment is highly prevalent following stroke and has significant functional impact (Tatemichi et al, 1994; Patel et al, 2003). Implementing an early cognitive screening strategy to identify problematic patients and implement interventions should reduce the long-term impact of cognitive deficits on functional recovery (Duits et al, 2008). Stroke cognitive screening can therefore provide invaluable data to improve stroke rehabilitation.

A number of organisations recommend routine cognitive screening of all stroke survivors (e.g. National Stroke Strategy, Scottish Intercollegiate Guideline Network, National Institute for Health and Care Excellence). Hospitals are increasingly implementing stroke cognitive screening and it may become a UK national audit standard. However, a lack of consensus remains around when and how to screen for cognitive function (Lees et al, 2012). This piece discusses five of the main questions around screening.

Should stroke cognitive screening occur?

Cognitive deficits following stroke are associated with negative treatment response and functional outcome. Stroke cognitive screening should help determine the presence (and nature) of cognitive impairments, to enable a more individualised stroke rehabilitation approach that accounts for specific cognitive deficits (Green et al, 2013).

However, care must be taken. Stroke patients often have a variety of disabilities that affect the cognition assessment process and the chosen screening tool's value; this includes cognitive function itself (Quaranta, 2008). Many stroke patients suffer from impaired attention, executive function, mental speed and language. Achieving a true measure of cognitive function can be problematic when the assessment itself requires

a high level of cognitive demand and/or verbal response. Transient cognitive dysfunction, aphasia and physical disability can give false positives for long-term cognitive impairment. Due to these disabilities, patients screened early could score poorly on assessments, despite higher levels of actual cognitive function (Lees et al, 2013). Thus, it is important that cognitive screening programmes are carefully designed, to ensure early comorbid stroke disabilities do not significantly interfere with the process.

When should stroke cognitive screening occur?

Following stroke, cognitive function often improves over time, and across domains (Hurford et al, 2013). Depending on stroke severity, patients may reach peak cognitive performance early or later post ictus, with recovery occurring in peaks and troughs or more gradually and continuously.

Two questions surround the implementation of an early stroke cognitive screening programme: (i) can it accurately measure the level of cognitive function post-stroke? (ii) can it accurately predict the peak functional level in recovery?

The best way to determine an optimum assessment point for stroke cognitive screening is for research to assess cognition at regular intervals over the first year in stroke cohorts to describe trends. If we can clarify when the majority of stroke survivors reach cognitive potential, we can then prospectively determine the most accurate timing for prediction. If this issue is not addressed and an early approach adopted then the majority of stroke survivors could screen positive for cognitive impairment. This could overload stroke services with patients who are not suitable for follow-up neuropsychological assessment.

While an early screening strategy aimed at implementing early intervention(s) might seem appealing, it may be impracticable and confer unfavourable

psychological and organisational outcomes. An inaccurate early diagnosis of cognitive impairment that spontaneously improves could be distressing to the patient and family. It could also lead to unnecessary medical investigations and treatments with unknown side effects, added organisational costs, and resources diverted from patients in actual need (Le Couteur et al, 2013). Arguably, until we better understand how patients' cognition improves over time, and until an accurate, reliable cognitive impairment measure is identified, cognitive screening after transient problems resolve may be preferable.

The majority of stroke patients are followed up medically after a few months, either by a specialised stroke service or their general practitioner. In the author's opinion, this would be an opportune time for screening assessments as the patient is likely back to a routine and more aware of what they can and cannot do.

Which psychometric measure(s) should be used?

Patients may be screened either directly, or indirectly using proxy questionnaires. Direct assessments tend to be favoured as it is assumed these provide a more accurate measure of specific cognitive domains. However, debate remains over which assessment approach is most reliable. Very few published works include neuropsychological measures and those that do are often not recognised as suitable for the stroke population. The lack of data surrounding norms across stroke patients at various stages in recovery in assessments makes it difficult to select a clinically appropriate assessment tool.

Available domain-based measures that show promise include the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Green et al, 2013), the Montreal Cognitive Assessment (MoCA) (Doong et al, 2010) and the Oxford Cognitive Screen (OCS). Difficulties can occur in

determining appropriate cut-off points that distinguish 'normal' cognitive function from a long-term cognitive deficit, even with detailed batteries, due to the lack of data on norms (Green et al, 2013).

Indeed, the long-term effect of cognitive impairment following stroke, although associated with negative outcome and poor recovery, is still under researched. Difficulties surrounding administration of cognitive assessment, poor understanding of the potential of the data collected, and time restraints in practice lie behind this lack of research.

If direct patient early screening is inappropriate due to transient or other issues interfering, a proxy screening strategy is necessary. Informant questionnaires provide details on patients' pre-stroke cognitive function and the extent of change post-stroke. Proxy questionnaires: are observational; can be more forgiving in the presence of other disabilities, such as aphasia; may reduce patient burden; and can be observed over time. A good assessment to determine patient cognition that accounts for previous capabilities is the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE). This short questionnaire can be filled in by any proxy in regular contact with the patient and gives a good feel for patient cognitive change over time, and it can screen for dementia.

Who should be responsible for stroke cognitive screening?

Although cognitive screening is important, uncertainty remains over the implications of gathered information for further care and personal responsibility. Cognitive assessment has to be consistent in its application to provide meaningful and comparable results across stroke cohorts. NHS improvement reports state that cognitive assessments have to be administered by an assessor with specific training in using those tool(s). This is a reasonable request but a lack of guidance, training and protocols for cognitive screening has left clinical teams without recommended assessments. Lack of available, trained assessors can lead to inaccurate administration or may result in the absence of screening.

Individual stroke services should ensure several members of the treat-

ing clinical team are trained in selected cognitive screening tools and have a protocol in place stating who is responsible for administering assessment(s). Training and oversight of cognition screening is arguably best handled by a clinical psychologist/neuropsychologist specialising in stroke although such individuals remain scarce. Clear definition by services of who is responsible for supervising and delivering cognition assessments should ensure more patients are screened. Stroke cognitive screening should, of course, involve all patients.

How should stroke screening data be interpreted?

Information extrapolated from cognitive screening can be useful to inform rehabilitation and/or grounds for referral to specialised services. It may allow therapists to modify a patient rehabilitation programme, and can provide useful data to help explain to patients and their families why some patients, while progressing physically, may still be struggling to complete basic activities of daily living.

It is important to understand that stroke cognitive screening data not only captures problematic areas requiring stroke rehabilitation team focus. Findings may also have significant implications for long-term care plans, support, and education to caregivers to enable a patient to live a maximally independent life post-discharge (Duits et al, 2008). Stroke cognitive screening assessments can be used to distinguish patients at high risk of further cognitive decline (vascular dementia) from those likely to make a reasonable cognitive recovery and resume pre-stroke function. By establishing which patients are at high risk of further cognitive decline, interventions to improve quality of life, allow planning and to slow down the rate of decline can be made available.

CONCLUSIONS

Stroke cognitive screening is complex and much remains to be determined. Domain-based cognitive measures that show promise are available (Doong et al, 2010; Green et al, 2013) and can help guide rehabilitation. However, the optimum point in the care pathway at which to introduce stroke cognitive screen-

ing is unknown and longitudinal observation research is needed to determine this. Over-diagnosis due to screening too early could overload services and prove financially, medically, psychologically, and socially detrimental. There is sparse evidence currently that early neuropsychological interventions assist although inter-disciplinary cognitive rehabilitation frameworks for stroke now exist (Taylor and Broomfield, 2013).

Better implementation of consistent cognitive assessments in research and practice should extend our understanding of which cognitive domains are usually affected early following stroke and which domain deficiencies predict long-term cognitive decline.

- Doong YH, Sharma VK, Poon Lap-Chan P, Venketasubramanian N, Teoh HL, Chee R et al (2010) The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci* **299**: 15–8
- Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ (2008) Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. *J Neurol Neurosurg Psychiatry* **79**(2): 143–6
- Green S, Sinclair E, Rodgers E, Birks E, Lincoln N (2013) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for post stroke cognitive impairment screening. *Int J Ther Rehabil* **20**(11): 7
- Hurford R, Charidimou A, Fox Z, Cipolotti L, Werring DJ (2013) Domain-specific trends in cognitive impairment after acute ischaemic stroke. *J Neurol* **260**(1): 237–41
- Le Couteur DG, Doust J, Creasey H, Brayne C (2013) Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis. *BMJ* **347**: 5125
- Lees R, Corbet S, Johnston C, Moffitt E, Shaw G, Quinn TJ (2013) Test accuracy of short screening tests for diagnosis of delirium or cognitive impairment in an acute stroke unit setting. *Stroke* **44**(11): 3078–83
- Lees R, Fearon P, Harrison JK, Broomfield NM, Quinn TJ (2012) Cognitive and mood assessment in stroke research: focused review of contemporary studies. *Stroke* **43**: 1678–80
- Patel M, Coshall C, Rudd AG, Wolfe CD (2003) Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clin Rehabil* **17**: 158–66
- Quaranta D, Marra C, Gainotti G (2008) Mood disorders after stroke: diagnostic validation of the poststroke depression rating scale. *Cerebrovasc Dis* **26**(3): 237–43
- Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E (1994) Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiatry* **57**(2): 202–7
- Taylor GH, Broomfield NM (2013) A Cognitive assessment and rehabilitation pathway for stroke (carps). *Top Stroke Rehabil* **20**(3): 270–82

Rosalind Lees¹, Niall M Broomfield^{1,2}
¹. Institute of Cardiovascular and Medical Sciences; ². Institute of Health and Well Being, College of Medical Veterinary and Life Sciences, University of Glasgow, UK.

Appendix O - The National Institutes of Health Stroke Scale

National Institutes of Health Stroke Scale score	
1a. Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b. Level of consciousness questions: What is the month? What is your age?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly
1c. Level of consciousness commands: Open and close your eyes. Grip and release your hand.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5. Motor arm 5a. Left arm 5b. Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement
6. Motor leg 6a. Left leg 6b. Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7. Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Total score = 0–42.	

0 = no stroke, 1-4 = minor stroke, 5-15 = moderate Stroke, 15-20 = moderate to severe stroke, 21-42 = severe stroke

Appendix P - The Cog-4 assessment, domains and scoring

Cog-4		Score
1(b)	Level of consciousness - questions (month and age)	
	Answers both correctly	0
	Answers one question correctly	1
	Answers neither questions correctly	2
1 (c)	Level of consciousness – commands (open and close eyes; grip and release hand)	
	Performs both task correctly	0
	Performs one task correctly	1
	Performs neither task correctly	2
9	Best language	
	No aphasia	0
	Mild to moderate aphasia	1
	Severe aphasia	2
	Mute and global aphasia	3
11	Extinction and inattention	
	No inattention	0
	Mild inattention	1
	Severe inattention	2

Appendix Q - The 4 'A's Test (4AT) for delirium screening

Assessment Domain	Domain Subsections	Score
ALERTNESS This includes patients who may be markedly drowsy (e.g. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.	Normal (fully alert, but not agitated, throughout assessment) Mild sleepiness for <10 seconds after waking, then normal Clearly abnormal	0 0 4
AMT 4 Age, date of birth, place (name of the hospital or building), current year.	No mistakes 1 mistake 2 or more mistakes/untestable	0 1 2
ATTENTION Ask the patient: "Please tell me the months of the year in backwards order, starting at December." To assist initial understanding one prompt of "what is the month before December?" is permitted.	Achieves 7 months or more correctly Starts but scores <7months/refuses to start Untestable (cannot start because unwell, drowsy, inattentive)	0 1 2
ACUTE CHANGE OR FLUCTUATING COURSE Evidence of significant change or fluctuation in: alertness, cognition, other mental function (e.g. paranoia, hallucinations) arising over the last two weeks and still evident in the last 24 hours.	Yes No	0 4
4AT SCORE TOTAL	4 or above: possible delirium +/- cognitive impairment 1-3: possible cognitive impairment 0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)	

GUIDANCE NOTES Version 1.1. Information and download: www.the4AT.com

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more suggests delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated solely on observation of the patient at the time of assessment. Item 4 requires information from one or more source(s), e.g. your own knowledge of the patient, other staff who know the patient (e.g. ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item.

AMT4 (Abbreviated Mental Test - 4): This score can be extracted from items in the AMT10 if the latter is done immediately before.

Acute Change or Fluctuating Course: Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, “Are you concerned about anything going on here?”; “Do you feel frightened by anything or anyone?”; “Have you been seeing or hearing anything unusual?”

Appendix R - The Abbreviated Mental Test (AMT)

ABBREVIATED MENTAL TEST (AMT)

The Abbreviated Mental Test Score (AMTS) was introduced by Hodkinson in 1972 to quickly assess elderly patients for the possibility of dementia. The test has utility across a range of acute and outpatient setting. It takes five minutes to administer and must include all 10 questions. A score of less than 7 or 8 suggests cognitive impairment.

QUESTION		Score 0 or 1
1.	How old are you?	
2.	What is the time (nearest hour)?	
3.	Address for recall at the end of test – this should be repeated by the patient, eg. 42 West Terrace	
4.	What year is it?	
5.	What is the name of this place?	
6.	Can the patient recognise two relevant persons (eg. nurse/doctor)	
7.	What was the date of your birth?	
8.	When was the second World War?	
9.	Who is the present Prime Minister?	
10.	Count down from 20 to 1 (no errors, no cues)	
TOTAL CORRECT		

Source: Hodkinson HM. (1972). Evaluation of a mental test score for assessment of mental impairment in the elderly. Age Ageing, 1:233-8.

Appendix S - The Short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

Short Form of the Informant Questionnaire On Cognitive Decline in the Elderly (IQCODE)

Informant ID:

Date Completed:

Researcher:

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now.

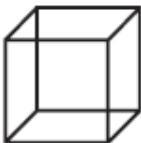
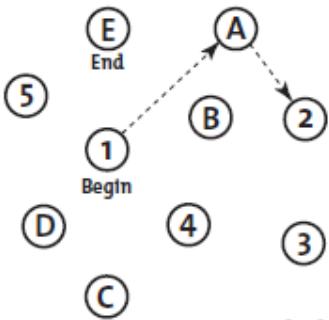



On the next page are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse than in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago.

So if 10 years ago this person always forgot where he/she had left things and he/she still does this, then this would be considered 'Not much change'. Please indicate the changes you have observed by ticking the appropriate box.

		Much improved	A bit improved	Not much change	A bit worse	Much worse
1	Remembering things about family and friends, e.g. occupations, birthdays, addresses					
2	Remembering things that have happened recently					
3	Recalling conversations a few days later					
4	Remembering her/his address and telephone number					
5	Remembering what day and month it is					
6	Remembering where things are usually kept					
7	Remembering where to find things which have been put in a different place from usual					
8	Knowing how to work familiar machines around the house					
9	Learning to use a new gadget or machine around the house					
10	Learning new things in general					
11	Following a story in a book or on TV					

1 2	Making decisions on everyday matters					
1 3	Handling money for shopping					
1 4	Handling financial matters, e.g. the pension, dealing with the bank					
1 5	Handling other everyday arithmetic problems, e.g. knowing how much food to buy, knowing how long between visits from family or friends					
1 6	Using his/her intelligence to understand what's going on and to reason things through					

Appendix T - The Montreal Cognitive Assessment (MoCA)

MONTELL COGNITIVE ASSESSMENT (MOCA)					NAME : _____	Education : _____	Date of birth : _____																					
SEX : _____					DATE : _____																							
VISUOSPATIAL / EXECUTIVE					Copy cube 		Draw CLOCK (Ten past eleven) (3 points)	POINTS ____/5																				
					<div style="display: flex; justify-content: space-around;"> [] [] </div>		<div style="display: flex; justify-content: space-around;"> [] [] [] </div>																					
NAMING									____/3																			
MEMORY					Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td>FACE</td> <td>VELVET</td> <td>CHURCH</td> <td>DAISY</td> <td>RED</td> </tr> <tr> <td>1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>			FACE	VELVET	CHURCH	DAISY	RED	1st trial						2nd trial						No points	
	FACE	VELVET	CHURCH	DAISY	RED																							
1st trial																												
2nd trial																												
ATTENTION					Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2		____/2																					
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B					____/1																							
Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt					____/3																							
LANGUAGE					Repeat : I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []		____/2																					
Fluency / Name maximum number of words in one minute that begin with the letter F [] _____ (N ≥ 11 words)					____/1																							
ABSTRACTION					Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler		____/2																					
DELAYED RECALL					Has to recall words WITH NO CUE		____/5																					
Optional					<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>FACE</td> <td>VELVET</td> <td>CHURCH</td> <td>DAISY</td> <td>RED</td> </tr> <tr> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> </tr> <tr> <td>Category cue</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Multiple choice cue</td> <td></td> <td></td> <td></td> <td></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	[]	[]	[]	[]	[]	Category cue					Multiple choice cue					Points for UNCUE recall only	
FACE	VELVET	CHURCH	DAISY	RED																								
[]	[]	[]	[]	[]																								
Category cue																												
Multiple choice cue																												
ORIENTATION					[] Date [] Month [] Year [] Day [] Place [] City		____/6																					

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www.mocatest.org

Normol ≥ 26 / 30

TOTAL

____/30

Administered by: _____

Add 1 point if ≤ 12 yr edu

Appendix U - The Confusion Assessment Method (CAM)

Confusion Assessment Method (CAM)

(Adapted from Inouye et al., 1990)

Patient's Name: _____ Date: _____

Instructions: Assess the following factors.

Acute Onset

1. Is there evidence of an acute change in mental status from the patient's baseline?
____ YES ____ NO ____ UNCERTAIN ____ NOT APPLICABLE

Inattention

(The questions listed under this topic are repeated for each topic where applicable.)

- 2A. Did the patient have difficulty focusing attention (for example, being easily distractible or having difficulty keeping track of what was being said)?
____ Not present at any time during interview
____ Present at some time during interview, but in mild form
____ Present at some time during interview, in marked form
____ Uncertain
- 2B. (If present or abnormal) Did this behavior fluctuate during the interview (that is, tend to come and go or increase and decrease in severity)?
____ YES ____ NO ____ UNCERTAIN ____ NOT APPLICABLE
- 2C. (If present or abnormal) Please describe this behavior.

Disorganized Thinking

3. Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable, switching from subject to subject?
____ YES ____ NO ____ UNCERTAIN ____ NOT APPLICABLE

Altered Level of Consciousness

4. Overall, how would you rate this patient's level of consciousness?
____ Alert (normal)
____ Vigilant (hyperalert, overly sensitive to environmental stimuli, startled very easily)
____ Lethargic (drowsy, easily aroused)
____ Stupor (difficult to arouse)
____ Coma (unarousable)
____ Uncertain

Disorientation

5. Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?
- ___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Memory Impairment

6. Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?
- ___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Perceptual Disturbances

7. Did the patient have any evidence of perceptual disturbances, such as hallucinations, illusions, or misinterpretations (for example, thinking something was moving when it was not)?
- ___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Psychomotor Agitation

- 8A. At any time during the interview, did the patient have an unusually increased level of motor activity, such as restlessness, picking at bedclothes, tapping fingers, or making frequent, sudden changes in position?
- ___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Psychomotor Retardation

- 8B. At any time during the interview, did the patient have an unusually decreased level of motor activity, such as sluggishness, staring into space, staying in one position for a long time, or moving very slowly?
- ___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Altered Sleep-Wake Cycle

9. Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?
- ___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Scoring:

For a diagnosis of delirium by CAM, the patient must display:

1. Presence of acute onset and fluctuating discourse

AND

2. Inattention

AND EITHER

3. Disorganized thinking

OR

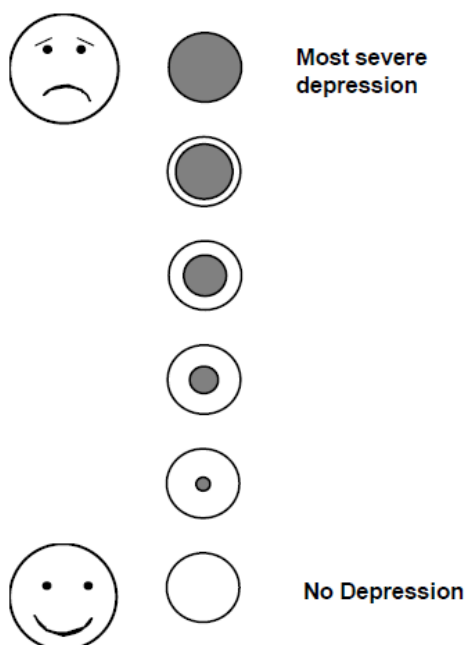
4. Altered level of consciousness

Source:

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990;113(12):941-948.

Appendix V - Depression Inventory Scale Circles (DISCS)

The Depression Intensity Scale Circles (DISCs) – pictorial version



The DISCs is displayed on a laminated card.

- Each circle is 2 cm in diameter.
- The scale measures 15 cm from the centre of the bottom circle to the centre of the top circle.
- A pictorial version also available.

Instructions for administration:

Say to the patient:

- This is a scale to measure depression
Please point to each of the circles in turn to make sure that you can see them all.
[Continue only if satisfactorily accomplished]
- The grey circles show how depressed you feel.
[Indicate the clear circle at the bottom]
- The bottom circle shows no depression.
[Indicate the fully shaded circle at the top]
- The top circle shows depression as bad as it can be.
[Pointing at each circle in ascending order]
- As you go from the bottom circle to the top, you can see that depression is becoming more and more severe.
- Which of these circles shows how depressed you feel today?

To the administrator:

In your opinion was the person able to understand this scale?





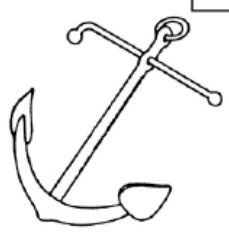
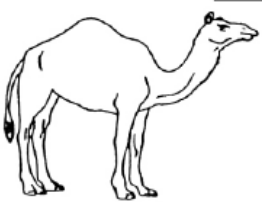

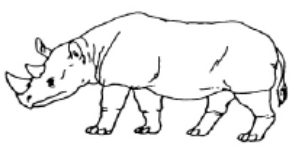



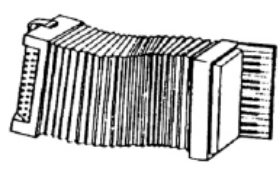
Yes ☐ No ☐

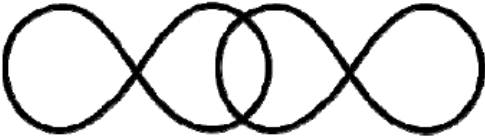
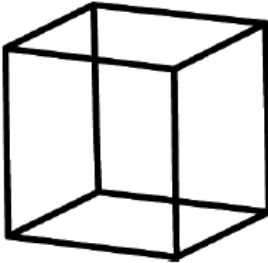
Comment

Appendix W - Addenbrookes' Cognitive Examination III (ACE-III)

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III English Version A (2012)																								
Name: _____ Date of Birth: _____ Hospital No. or Address: _____			Date of testing: ____/____/____ Tester's name: _____ Age at leaving full-time education: _____ Occupation: _____ Handedness: _____																					
ATTENTION																								
➤ Ask: What is the	Day	Date	Month	Year	Season	Attention [Score 0-5] <input type="text"/>																		
➤ Ask: Which	No./Floor	Street/Hospital	Town	County	Country	Attention [Score 0-5] <input type="text"/>																		
ATTENTION																								
➤ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later". ➤ Score <i>only</i> the first trial (repeat 3 times if necessary). ➤ Register number of trials: _____						Attention [Score 0-3] <input type="text"/>																		
ATTENTION																								
➤ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop." ➤ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4). ➤ Stop after five subtractions (93, 86, 79, 72, 65): _____						Attention [Score 0-5] <input type="text"/>																		
MEMORY																								
➤ Ask: 'Which 3 words did I ask you to repeat and remember?' _____						Memory [Score 0-3] <input type="text"/>																		
FLUENCY																								
➤ Letters Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".						Fluency [Score 0 – 7] <input type="text"/>																		
						<table border="1"> <tr><td>≥ 18</td><td>7</td></tr> <tr><td>14-17</td><td>6</td></tr> <tr><td>11-13</td><td>5</td></tr> <tr><td>8-10</td><td>4</td></tr> <tr><td>6-7</td><td>3</td></tr> <tr><td>4-5</td><td>2</td></tr> <tr><td>2-3</td><td>1</td></tr> <tr><td>0-1</td><td>0</td></tr> <tr><td>total</td><td>correct</td></tr> </table>	≥ 18	7	14-17	6	11-13	5	8-10	4	6-7	3	4-5	2	2-3	1	0-1	0	total	correct
≥ 18	7																							
14-17	6																							
11-13	5																							
8-10	4																							
6-7	3																							
4-5	2																							
2-3	1																							
0-1	0																							
total	correct																							
➤ Animals Say: "Now can you name as many animals as possible. It can begin with any letter."						Fluency [Score 0 – 7] <input type="text"/>																		
						<table border="1"> <tr><td>≥ 22</td><td>7</td></tr> <tr><td>17-21</td><td>6</td></tr> <tr><td>14-16</td><td>5</td></tr> <tr><td>11-13</td><td>4</td></tr> <tr><td>9-10</td><td>3</td></tr> <tr><td>7-8</td><td>2</td></tr> <tr><td>5-6</td><td>1</td></tr> <tr><td><5</td><td>0</td></tr> <tr><td>total</td><td>correct</td></tr> </table>	≥ 22	7	17-21	6	14-16	5	11-13	4	9-10	3	7-8	2	5-6	1	<5	0	total	correct
≥ 22	7																							
17-21	6																							
14-16	5																							
11-13	4																							
9-10	3																							
7-8	2																							
5-6	1																							
<5	0																							
total	correct																							

MEMORY				
<p>➤ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."</p> <p>Score only the third trial.</p>				<p>Memory [Score 0 – 7]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
	1st Trial	2nd Trial	3rd Trial	
Harry Barnes 73 Orchard Close Kingsbridge Devon	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	
MEMORY				
<p>➤ Name of the current Prime Minister.....</p> <p>➤ Name of the woman who was Prime Minister</p> <p>➤ Name of the USA president.....</p> <p>➤ Name of the USA president who was assassinated in the 1960s.....</p>				<p>Memory [Score 0 – 4]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
LANGUAGE				
<p>➤ Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject to "Pick up the pencil and then the paper." If incorrect, score 0 and do not continue further.</p> <p>➤ If the subject is correct on the practice trial, continue with the following three commands below.</p> <ul style="list-style-type: none"> • Ask the subject to "Place the paper on top of the pencil" • Ask the subject to "Pick up the pencil but not the paper" • Ask the subject to "Pass me the pencil after touching the paper" <p>Note: Place the pencil and paper in front of the subject before each command.</p>				<p>Language [Score 0-3]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
LANGUAGE				
<p>➤ Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/Christmas. Write in complete sentences and do not use abbreviations. Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.</p>				<p>Language [Score 0-2]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
LANGUAGE				
<p>➤ Ask the subject to repeat: 'caterpillar'; 'eccentricity'; 'unintelligible'; 'statistician'</p> <p>Score 2 if all are correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.</p>				<p>Language [Score 0-2]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>

LANGUAGE	
<p>➤ Ask the subject to repeat: 'All that glitters is not gold'</p>	<p>Language [Score 0-1]</p> <div></div>
<p>➤ Ask the subject to repeat: 'A stitch in time saves nine'</p>	<p>Language [Score 0-1]</p> <div></div>
LANGUAGE	
<p>➤ Ask the subject to name the following pictures:</p> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div> <div> <div>_____ <div></div></div>  </div>	<p>Language [Score 0-12]</p> <div></div>
LANGUAGE	
<p>➤ Using the pictures above, ask the subject to:</p> <ul style="list-style-type: none"> • Point to the one which is associated with the monarchy • Point to the one which is a marsupial • Point to the one which is found in the Antarctic • Point to the one which has a nautical connection 	<p>Language [Score 0-4]</p> <div></div>

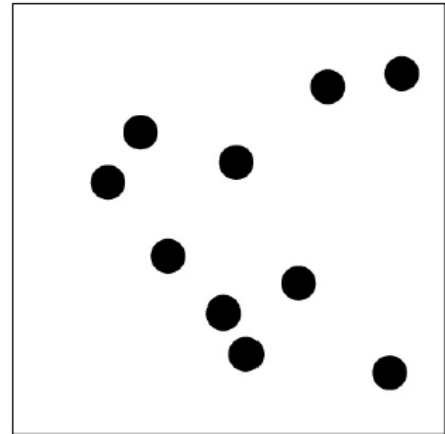
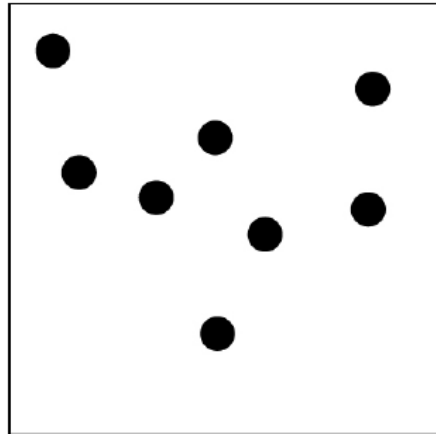
LANGUAGE	
<p>➤ Ask the subject to read the following words: (Score 1 only if all correct)</p> <p style="text-align: center;"> sew pint soot dough height </p>	<p>Language [Score 0-1]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin-left: auto;"></div>
VISUOSPATIAL ABILITIES	
<p>➤ Infinity Diagram: Ask the subject to copy this diagram</p>	<p>Visuospatial [Score 0-1]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin-left: auto;"></div>
	
<p>➤ Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide).</p>	<p>Visuospatial [Score 0-2]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin-left: auto;"></div>
	
<p>➤ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct).</p>	<p>Visuospatial [Score 0-5]</p> <div style="border: 1px solid black; width: 40px; height: 20px; margin-left: auto;"></div>

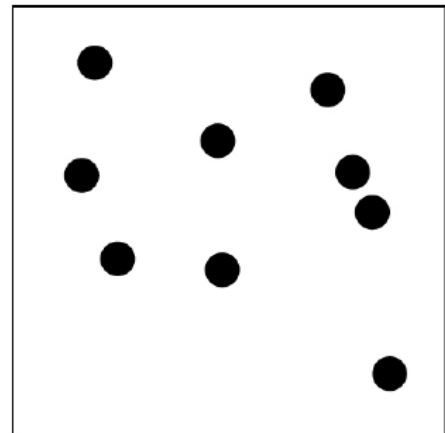
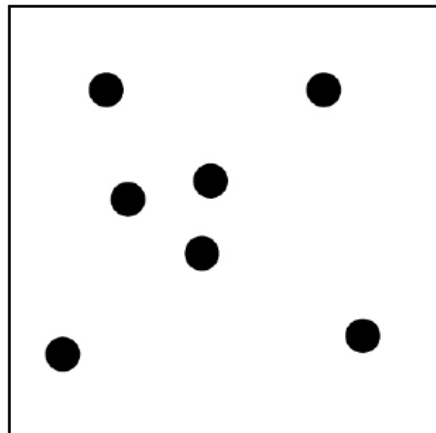
Updated 20/11/2012

VISUOSPATIAL ABILITIES

➤ Ask the subject to count the dots without pointing to them




Visuospatial
[Score 0-4]





VISUOSPATIAL ABILITIES					
➤ Ask the subject to identify the letters					Visuospatial [Score 0-4] <input style="width: 40px;" type="text"/>
		<input style="width: 40px; height: 20px;" type="text"/>			<input style="width: 40px; height: 20px;" type="text"/>
		<input style="width: 40px; height: 20px;" type="text"/>			<input style="width: 40px; height: 20px;" type="text"/>
MEMORY					
➤ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"					
Harry Barnes 73 Orchard Close Kingsbridge Devon				Memory [Score 0-7] <input style="width: 40px;" type="text"/>
MEMORY					
➤ This test should be done if the subject failed to recall one or more items above. If all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.					Memory [Score 0-5] <input style="width: 40px;" type="text"/>
Jerry Barnes		Harry Barnes		Harry Bradford	recalled
37		73		76	recalled
Orchard Place		Oak Close		Orchard Close	recalled
Oakhampton		Kingsbridge		Dartington	recalled
Devon		Dorset		Somerset	recalled
SCORES					
TOTAL ACE-III SCORE					/100
Attention					/18
Memory					/26
Fluency					/14
Language					/26
Visuospatial					/16

Appendix X - Good clinical practice certificate

<input type="checkbox"/> <input type="checkbox"/>		
<p align="center">Certificate of Attendance This is to Certify</p>		
<p align="center">Rosalind Lees</p>		
<p align="center">Attended the 1 day course</p>		
<p align="center">Introduction to Good Clinical Practice</p>		
<p align="center">16th January 2013</p>		
<p align="center"><u>Course Content</u></p>		
<ul style="list-style-type: none"> • History of Clinical Trials and the Development of GCP • Informed Consent • Pharmacovigilance • Responsibilities of Research Personnel • Monitoring • Evaluation 		
<p>Signed </p> <p>Shona McDermott Assistant Director of CRF, Education & Training</p>		
<p>GCPD Credits: 6 Category: 1 (external) RCP Active Code No: 78844 Approved by the Federation of the Royal Colleges of Physicians of the United Kingdom</p>		
<p>Glasgow Clinical Research Facility Tennent Building 33 Church Street Glasgow G1 1 9NY</p>		

Appendix Y - Rankin scale clinical trials 1st training certification

1/21/13

Certificate



EUROHYP-1



Certificate of Completion

Rosalind Lees

Has successfully completed

A004 - Rankin Scale Clinical Trials - 1st. Certification -AB V.1

This course module contains 2 groups of patients, 9 (nine) patients in total, which must be properly analyzed and successfully score in order to use this certification program for your clinical trials, (CERTIFICATE VALID FOR UP TO TWO (2) YEARS FROM THE DATE OF COMPLETION) © Ken Lees, MD, University of Glasgow -2009-Present All Rights Reserved

on

Monday, January 21, 2013 at 6:55 AM CST

Appendix Z - Addenbrokes' Cognitive Examination-III training certificate



Bibliography

1. World Health Organisation (WHO). Annex Table 2: Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002. In: Organisation Wh, editor. Geneva World Health Organisation 2004.
2. Feigin VL. Stroke epidemiology in the developing world. *Lancet*. 2005;365(9478):2160-1.
3. Chiu D, Peterson L, Elkind MS, Rosand J, Gerber LM, Silverstein MD. Comparison of outcomes after intracerebral hemorrhage and ischemic stroke. *J Stroke Cerebrovasc Dis*. 2010;19(3):225-9.
4. Rathore SS, Hinn AR, Cooper LS, Tyroler HA, Rosamond WD. Characterization of incident stroke signs and symptoms: findings from the atherosclerosis risk in communities study. *Stroke*. 2002;33(11):2718-21.
5. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. *Stroke*. 2009;40(6):2068-72.
6. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19(12):1497-500.
7. European Cardiovascular Disease Statistics [Internet]. British Heart Foundation Health promotion Research Group 2000.
8. Duncan PW, Goldstein LB, Horner RD, Landsman PB, Samsa GP, Matchar DB. Similar motor recovery of upper and lower extremities after stroke. *Stroke*. 1994;25(6):1181-8.
9. Sturm JW, Dewey HM, Donnan GA, Macdonell RA, McNeil JJ, Thrift AG. Handicap after stroke: how does it relate to disability, perception of recovery, and stroke subtype?: the north North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke*. 2002;33(3):762-8.
10. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. *Stroke*. 2001;32(6):1279-84.
11. Stroke Association. Stroke Statistics. A01R11 [Internet]. 2013 May 2014:[13 p.]. Available from: <http://www.stroke.org.uk/resource-sheet/stroke-statistics>.
12. Bueno VF, Brunoni AR, Boggio PS, Bensenor IM, Fregni F. Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression. *Neurocase*. 2011;17(4):318-22.
13. Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments. *Lancet neurology*. 2008;7(3):246-55.
14. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiatry*. 1994;57(2):202-7.
15. Hurford R, Charidimou A, Fox Z, Cipolotti L, Werring DJ. Domain-specific trends in cognitive impairment after acute ischaemic stroke. *J Neurol*. 2013;260(1):237-41.
16. Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: still an incomplete picture. *International journal of stroke : official journal of the International Stroke Society*. 2013;8(1):38-45.

17. Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. *Lancet neurology*. 2005;4(11):752-9.
18. Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. *International Journal of Stroke*. 2012;8(7):545-9.
19. Broomfield NM, Laidlaw K, Hickabottom E, Murray MF, Pendrey R, Whittick JE, et al. Post-stroke depression: the case for augmented, individually tailored cognitive behavioural therapy. *Clin Psychol Psychother*. 2011;18(3):202-17.
20. Andersen G, Vestergaard K, Ingemann-Nielsen M, Lauritzen L. Risk factors for post-stroke depression. *Acta Psychiatr Scand*. 1995;92(3):193-8.
21. Allan LM, Rowan EN, Thomas AJ, Polvikoski TM, O'Brien JT, Kalaria RN. Long-term incidence of depression and predictors of depressive symptoms in older stroke survivors. *Br J Psychiatry*. 2013;203(6):453-60.
22. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke*. 2006;37(9):2220-41.
23. Danovska M, Stamenov B, Alexandrova M, Peychinska D. Post-stroke cognitive impairment- Phenomenology and prognostic factors. *Journal of International Medical Association Bulgaria*. 2012;18(Book 3):8.
24. McManus J, Pathansali R, Hassan H, Ouldred E, Cooper D, Stewart R, et al. The course of delirium in acute stroke. *Age and ageing*. 2009;38(4):385-9.
25. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: a systematic review and meta-analysis. *Stroke*. 2012;43(3):645-9.
26. Melkas S, Laurila JV, Vataja R, Oksala N, Jokinen H, Pohjasvaara T, et al. Post-stroke delirium in relation to dementia and long-term mortality. *Int J Geriatr Psychiatry*. 2012;27(4):401-8.
27. MacLulich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long-term cognitive impairment. *Int Rev Psychiatry*. 2009;21(1):30-42.
28. McManus J, Pathansali R, Stewart R, Macdonald A, Jackson S. Delirium post-stroke. *Age and ageing*. 2007;36(6):613-8.
29. Camus V, Gonthier R, Dubos G, Schwed P, Simeone I. Etiologic and outcome profiles in hypoactive and hyperactive subtypes of delirium. *Journal of geriatric psychiatry and neurology*. 2000;13(1):38-42.
30. England N. CQUIN Dementia In: Improvement Ifla, editor.: NHS England Institute for Innovation and Improvement ; 2012/13.
31. Wade DT. Measurement in neurological rehabilitation. *Current opinion in neurology and neurosurgery*. 1992;5(5):682-6.
32. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age and ageing*. 2006;35(4):350-64.
33. Young J, Inouye SK. Delirium in older people. *Bmj*. 2007;334(7598):842-6.
34. Henon H, Lebert F, Durieu I, Godefroy O, Lucas C, Pasquier F, et al. Confusional state in stroke: relation to preexisting dementia, patient characteristics, and outcome. *Stroke*. 1999;30(4):773-9.

35. Sheng A, Shen Q, Cordato D, Zhang Y, Yin Chan D. Delirium within three days of stroke in a cohort of elderly patients. *Journal of American Geriatric Society*. 2006;54(8):7.
36. Melkas S, HJokinen H, Hietanen M, Erkinjuntti T. Poststroke cognitive impairment and dementia: prevalence, diagnosis and treatment. *Degenerative Neurological and Neuromuscular Disease*. 2014;4:7.
37. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT) phase II safety and feasibility. *Stroke*. 2008;39(2):390-6.
38. Rostamian S, Mahinrad S, Stijnen T, Sabayan B, de Craen AJ. Cognitive Impairment and Risk of Stroke: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Stroke*. 2014.
39. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262-70.
40. Feldman HH, Jacova C. Mild cognitive impairment. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2005;13(8):645-55.
41. Kwa VIH, Limburg M, Voogel AJ, Teunisse S, Derix MMA, Hijdra A. Feasibility of cognitive screening of patients with ischaemic stroke using the CAMCOG - A hospital-based study. *Journal of Neurology*. 1996;243(5):405-9.
42. Bernhardt J, Indredavik B, Langhorne P. When should rehabilitation begin after stroke? *International Journal of Stroke*. 2013;8(1):5-7.
43. Chertkow H. Mild cognitive impairment. *Current opinion in neurology*. 2002;15(4):401-7.
44. Ferro JM, Caeiro L, Verdelho A. Delirium in acute stroke. *Current opinion in neurology*. 2002;15(1):51-5.
45. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Archives of neurology*. 1999;56(3):303-8.
46. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet neurology*. 2003;2(1):15-21.
47. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *The American journal of psychiatry*. 1983;140(6):734-9.
48. Research CfIPH. The Centre for Epidemiological Studies Depression Scale Revised (CESD-R) [cited 2014 10/07/14]. Available from: <http://cesd-r.com/>.
49. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. *QJM : monthly journal of the Association of Physicians*. 2007;100(8):469-84.
50. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-7.
51. Society As. Helping you to assess cognition: A practical toolkit for clinicians. In: Health Do, editor. <http://www.alzheimers.org.uk/cognitiveassessment>. Alzheimer's Society; 2013. p. 43.
52. World Health Organisation (WHO). The world health report: Shaping the future Geneva WHO; 2003. p. 1-204.
53. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet neurology*. 2009;8(11):1006-18.

54. van der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. *J Neurol Neurosurg Psychiatry*. 2005;76 Suppl 5:v2-7.
55. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends in Pharmacological Sciences*. 1991;12(10):383-8.
56. Mudher A, Lovestone S. Alzheimer's disease-do tauists and baptists finally shake hands? *Trends Neurosci*. 2002;25(1):22-6.
57. GomezIsla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol*. 1997;41(1):17-24.
58. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-6.
59. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. *Archives of neurology*. 2004;61(3):378-84.
60. Roberts RE. Reliability of the CES-D Scale in different ethnic contexts. *Psychiatry research*. 1980;2(2):125-34.
61. McCullagh C, Craig D, McIlroy S, Passmore A. Risk factors for dementia. *Advances in Psychiatric Treatment*. 2001;7:8.
62. Duyckaerts C, Colle MA, Dessi F, Grignon Y, Piette F, Hauw JJ. The progression of the lesions in Alzheimer disease: insights from a prospective clinicopathological study. *J Neural Transm Suppl*. 1998;53:119-26.
63. Kalaria RN, Bhatti SU, Lust WD, Perry G. The amyloid precursor protein in ischemic brain injury and chronic hypoperfusion. *Ann N Y Acad Sci*. 1993;695:190-3.
64. Jorm AF. History of depression as a risk factor for dementia: an updated review. *The Australian and New Zealand journal of psychiatry*. 2001;35(6):776-81.
65. Speck CE, Kukull WA, Brenner DE, Bowen JD, McCormick WC, Teri L, et al. History of Depression as a Risk Factor for Alzheimers-Disease. *Epidemiology*. 1995;6(4):366-9.
66. Stephens S, Kenny RA, Rowan E, Kalaria RN, Bradbury M, Pearce R, et al. Association between mild vascular cognitive impairment and impaired activities of daily living in older stroke survivors without dementia. *Journal of the American Geriatrics Society*. 2005;53(1):103-7.
67. Zinn S, Dudley TK, Bosworth HB, Hoenig HM, Duncan PW, Horner RD. The effect of poststroke cognitive impairment on rehabilitation process and functional outcome. *Archives of physical medicine and rehabilitation*. 2004;85(7):1084-90.
68. Heruti RJ, Lusky A, Dankner R, Ring H, Dolgopiat M, Barell V, et al. Rehabilitation outcome of elderly patients after a first stroke: effect of cognitive status at admission on the functional outcome. *Archives of Physical Medical Rehabilitation*. 2002;83(6):742-9.
69. Galski T, Bruno RL, Zorowitz R, Walker J. Predicting length of stay, functional outcome, and aftercare in the rehabilitation of stroke patients. The dominant role of higher-order cognition. *Stroke*. 1993;24(12):1794-800.
70. Boyd JH, Weissman MM, Thompson WD, Myers JK. Screening for depression in a community sample. Understanding the discrepancies between depression symptom and diagnostic scales. *Arch Gen Psychiatry*. 1982;39(10):1195-200.

71. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and Validation of a Geriatric Depression Screening Scale - a Preliminary-Report. *J Psychiat Res.* 1983;17(1):37-49.
72. Leshner EL, Berryhill JS. Validation of the Geriatric Depression Scale--Short Form among inpatients. *Journal of clinical psychology.* 1994;50(2):256-60.
73. del Ser T, Barba R, Morin MM, Domingo J, Cemillan C, Pondal M, et al. Evolution of cognitive impairment after stroke and risk factors for delayed progression. *Stroke.* 2005;36(12):2670-5.
74. Nys GM, van Zandvoort MJ, de Kort PL, van der Worp HB, Jansen BP, Algra A, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology.* 2005;64(5):821-7.
75. Hochstenbach J, Mulder T, van Limbeek J, Donders R, Schoonderwaldt H. Cognitive decline following stroke: a comprehensive study of cognitive decline following stroke. *Journal of Clinical Experimental Neuropsychology.* 1998;20(4):503-17.
76. Pendlebury ST, Wadling S, Silver LE, Mehta Z, Rothwell PM. Transient cognitive impairment in TIA and minor stroke. *Stroke.* 2011;42(11):3116-21.
77. Bowler JV, Hadar U, Wade JP. Cognition in stroke. *Acta neurologica Scandinavica.* 1994;90(6):424-9.
78. Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, Wen W, et al. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. *Neurology.* 2004;62(6):912-9.
79. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. *Stroke.* 2005;36(6):1330-40.
80. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke.* 2005;36(10):2296-301.
81. House A. Mood Disorders after Stroke - a Review of the Evidence. *Int J Geriatr Psych.* 1987;2(4):211-21.
82. House A, Dennis M, Molyneux A, Warlow C, Hawton K. Emotionalism after stroke. *Bmj.* 1989;298(6679):991-4.
83. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke.* 1993;24(7):976-82.
84. Williams LS, Ghose SS, Swindle RW. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. *The American journal of psychiatry.* 2004;161(6):1090-5.
85. Babulal GM, Huskey TN, Roe CM, Goette SA, Connor LT. Cognitive impairments and mood disruptions negatively impact instrumental activities of daily living performance in the first three months after a first stroke. *Top Stroke Rehabil.* 2015;22(2):144-51.
86. Robinson RG, Jorge RE. Post-Stroke Depression: A Review. *The American journal of psychiatry.* 2015;appiajp201515030363.
87. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. Aging, memory, and mild cognitive impairment. *Int Psychogeriatr.* 1997;9 Suppl 1:65-9.
88. Barker-Collo SL. Depression and anxiety 3 months post stroke: Prevalence and correlates. *Arch Clin Neuropsych.* 2007;22(4):519-31.

89. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009;119(4):252-65.
90. Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. *International Journal of Stroke*. 2013;8(7):5.
91. Elisei S, Pauselli L, Balducci PM, Moretti P, Quartesan R. Mood disorders in general hospital inpatients: one year data from a psychiatric consultation-liaison service. *Psychiatr Danub*. 2013;25 Suppl 2:S268-71.
92. Mago R, Gomez JP, Gupta N, Kunhel EJ. Anxiety in medically ill patients. *Curr Psychiatry Rep*. 2006;8(3):228-33.
93. Lerdal A, Bakken LN, Rasmussen EF, Beiermann C, Ryen S, Pynten S, et al. Physical impairment, depressive symptoms and pre-stroke fatigue are related to fatigue in the acute phase after stroke. *Disabil Rehabil*. 2011;33(4):334-42.
94. Paolucci S. Epidemiology and treatment of post-stroke depression. *Neuropsychiatr Dis Treat*. 2008;4(1):145-54.
95. Laures-Gore JS, DeFife LC. Perceived stress and depression in left and right hemisphere post-stroke patients. *Neuropsychol Rehabil*. 2013;23(6):783-97.
96. Thomas SA, Lincoln NB. Factors relating to depression after stroke. *Br J Clin Psychol*. 2006;45(Pt 1):49-61.
97. Pohjasvaara T, Leppavuori A, Siira I, Vataja R, Kaste M, Erkinjuntti T. Frequency and clinical determinants of poststroke depression. *Stroke*. 1998;29(11):2311-7.
98. Wade DT, Legh-Smith J, Hewer RA. Depressed mood after stroke. A community study of its frequency. *Br J Psychiatry*. 1987;151:200-5.
99. Downhill JE, Jr., Robinson RG. Longitudinal assessment of depression and cognitive impairment following stroke. *J Nerv Ment Dis*. 1994;182(8):425-31.
100. De Ryck A, Brouns R, Fransen E, Geurden M, Van Gestel G, Wilssens I, et al. A prospective study on the prevalence and risk factors of poststroke depression. *Cerebrovascular diseases extra*. 2013;3(1):1-13.
101. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2013;9(1):63-75 e2.
102. Poeck K. Pathophysiology of emotional disorders associated with brain damage. In: Vinken P, Bruyn G, editors. *Handbook of clinical neurology*. Holland: North Holland Publishing; 1969.
103. Kim JS. Poststroke emotional incontinence: is it depression? *Current neurology and neuroscience reports*. 2012;12(6):629-30.
104. Choi-Kwon S, Han K, Choi S, Suh M, Kim YJ, Song H, et al. Poststroke depression and emotional incontinence: factors related to acute and subacute stages. *Neurology*. 2012;78(15):1130-7.
105. Tang WK, Chen YK, Lu JY, Mok VC, Xiang YT, Ungvari GS, et al. Microbleeds and post-stroke emotional lability. *J Neurol Neurosurg Psychiatry*. 2009;80(10):1082-6.
106. Schmahmann JD. Vascular syndromes of the thalamus. *Stroke*. 2003;34(9):2264-78.

107. Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, et al. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. *Brain*. 2004;127(Pt 10):2265-75.
108. Broomfield NM, Scoular A, Welsh P, Walters M, Evans JJ. Poststroke anxiety is prevalent at the population level, especially among socially deprived and younger age community stroke survivors. *International journal of stroke : official journal of the International Stroke Society*. 2013.
109. Ahlsio B, Britton M, Murray V, Theorell T. Disablement and quality of life after stroke. *Stroke*. 1984;15(5):886-90.
110. Thompson S. Rehabilitation of cognitive and emotional problems following stroke In: Fawcus R, editor. *Stroke rehabilitation: A collaborative approach*. Oxford Blackwell; 2000. p. 13.
111. Reid A, Chesson R. Goal Attainment Scaling: Is it appropriate for stroke patients and their physiotherapists? *Physiotherapy*. 1998;84(3):9.
112. Schmid AA, Acuff M, Doster K, Gwaltney-Duiser A, Whitaker A, Damush T, et al. Poststroke fear of falling in the hospital setting. *Top Stroke Rehabil*. 2009;16(5):357-66.
113. Townend E, Tinson D, Kwan J, Sharpe M. Fear of recurrence and beliefs about preventing recurrence in persons who have suffered a stroke. *J Psychosom Res*. 2006;61(6):747-55.
114. Castillo CS, Starkstein SE, Fedoroff JP, Price TR, Robinson RG. Generalized anxiety disorder after stroke. *J Nerv Ment Dis*. 1993;181(2):100-6.
115. Astrom M. Generalized anxiety disorder in stroke patients - A 3-year longitudinal study. *Stroke*. 1996;27(2):270-5.
116. Starkstein SE, Cohen BS, Fedoroff P, Parikh RM, Price TR, Robinson RG. Relationship between Anxiety Disorders and Depressive-Disorders in Patients with Cerebrovascular Injury. *Arch Gen Psychiat*. 1990;47(3):246-51.
117. Tang WK, Chen Y, Lu J, Liang H, Chu WC, Tong Mok VC, et al. Frontal infarcts and anxiety in stroke. *Stroke*. 2012;43(5):1426-8.
118. Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. *Stroke*. 2004;35(3):794-802.
119. Taylor GH, Todman J, Broomfield NM. Post-stroke emotional adjustment: a modified Social Cognitive Transition model. *Neuropsychol Rehabil*. 2011;21(6):808-24.
120. Brennan J. Adjustment to cancer - coping or personal transition? *Psycho-oncology*. 2001;10(1):1-18.
121. American Psychiatric Association, editor. *Diagnostic and statistical manual of mental disorders*. Fourth Edition, Text Revision ed. Washington, DC: American Psychiatric Association; 2000.
122. Carta MG, Balestrieri M, Murru A, Hardoy MC. Adjustment Disorder: epidemiology, diagnosis and treatment. *Clinical practice and epidemiology in mental health : CP & EMH*. 2009;5:15.
123. Despland JN, Monod L, Ferrero F. Clinical relevance of adjustment disorder in DSM-III-4 and DSM-IV. *Comprehensive psychiatry*. 1995;36(6):454-60.

124. Sarre S, Redlich C, Tinker A, Sadler E, Bhalla A, McKeivitt C. A systematic review of qualitative studies on adjusting after stroke: lessons for the study of resilience. *Disabil Rehabil.* 2014;36(9):716-26.
125. Mumby K, Whitworth A. Adjustment processes in chronic aphasia after stroke: Exploring multiple perspectives in the context of a community-based intervention. *Aphasiology.* 2013;27(4):462-89.
126. Anson K, Ponsford J. Coping and emotional adjustment following traumatic brain injury. *The Journal of head trauma rehabilitation.* 2006;21(3):248-59.
127. Bossuyt P, Davenport C, Deeks J, Hyde C, Leeflang M, Scholten R. Interpreting results and drawing conclusions. 2013. In: *Cochrane handbook for systematic reviews of diagnostic test accuracy* [Internet]. The Cochrane Collaboration; [31].
128. Hofer H, Holtforth MG, Frischknecht E, Znoj HJ. Fostering adjustment to acquired brain injury by psychotherapeutic interventions: a preliminary study. *Applied neuropsychology.* 2010;17(1):18-26.
129. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis.* 2001;12(2):75-81.
130. Carlsson GE, Moller A, Blomstrand C. Consequences of mild stroke in persons <75 years -- a 1-year follow-up. *Cerebrovasc Dis.* 2003;16(4):383-8.
131. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke.* 2002;33(5):1327-33.
132. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Archives of physical medicine and rehabilitation.* 1999;80(2):173-8.
133. van der Werf SP, van den Broek HL, Anten HW, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *European neurology.* 2001;45(1):28-33.
134. Radman N, Staub F, Aboulafia-Brakha T, Berney A, Bogousslavsky J, Annoni JM. Poststroke fatigue following minor infarcts: a prospective study. *Neurology.* 2012;79(14):1422-7.
135. Wu S, Barugh A, Macleod M, Mead G. Psychological Associations of Poststroke Fatigue: A Systematic Review and Meta-Analysis. *Stroke.* 2014.
136. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *International Journal of Stroke.* 2014.
137. Morris PLP, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of Depression with 10-Year Poststroke Mortality. *American Journal of Psychiatry.* 1993;150(1):124-9.
138. House A, Dennis M, Mogridge L, Warlow C, Hawton K, Jones L. Mood disorders in the year after first stroke. *Br J Psychiatry.* 1991;158:83-92.
139. House A, Knapp P, Bamford J, Vail A. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. *Stroke.* 2001;32(3):696-701.
140. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* 2013;35(4):291-9.

141. Kauhanen ML, Korpelainen JT, Hiltunen P, Nieminen P, Sotaniemi KA, Myllyla VV. Domains and determinants of quality of life after stroke caused by brain infarction. *Archives of physical medicine and rehabilitation*. 2000;81(12):1541-6.
142. Choi DH, Jeong BO, Kang HJ, Kim SW, Kim JM, Shin IS, et al. Psychiatric comorbidity and quality of life in patients with post-stroke emotional incontinence. *Psychiatry investigation*. 2013;10(4):382-7.
143. Chemerinski E, Robinson RG, Kosier JT. Improved recovery in activities of daily living associated with remission of poststroke depression. *Stroke*. 2001;32(1):113-7.
144. Parikh RM, Robinson RG, Lipsey JR, Starkstein SE, Fedoroff JP, Price TR. The Impact of Poststroke Depression on Recovery in Activities of Daily Living over a 2-Year Follow-Up. *Archives of neurology*. 1990;47(7):785-9.
145. Pohjasvaara T, Vataja R, Leppavuori A, Kaste M, Erkinjuntti T. Depression is an independent predictor of poor long-term functional outcome post-stroke. *European Journal of Neurology*. 2001;8(4):315-9.
146. Sinyor D, Amato P, Kaloupek DG, Becker R, Goldenberg M, Coopersmith H. Post-stroke depression: relationships to functional impairment, coping strategies, and rehabilitation outcome. *Stroke*. 1986;17(6):1102-7.
147. St George B, Pollock A, Firkins L. Research priorities related to stroke: results of a James Lind Alliance priority setting project. *International Journal of Stroke*. 2011;6 (suppl 2):2.
148. Hachinski V. The 2005 Thomas Willis Lecture: stroke and vascular cognitive impairment: a transdisciplinary, translational and transactional approach. *Stroke*. 2007;38(4):1396.
149. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, et al. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. *Stroke*. 2010;41(10):2402-48.
150. Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke. Rehabilitation, prevention and management of complications and discharge planning In: Network SIG, editor.: SIGN publication Guideline 2010.
151. Brunet MD, McCartney M, Heath I, Tomlinson J, Cosgrove J, Deveson P, et al. Open letter to the prime minister and chief medical officer for England. There is no evidence base for proposed dementia screening. *Bmj*. 2012;345(e8588).
152. Le Couteur DG, Doust J, Creasey H, Brayne C. Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis. *Bmj*. 2013;347:f5125.
153. Quinn TJ, Dawson J, Walters MR, Lees KR. Functional outcome measures in contemporary stroke trials. *International journal of stroke : official journal of the International Stroke Society*. 2009;4(3):200-5.
154. The Internet Stroke Centre. Stroke Assessment Scales <http://www.strokecenter.org/1997-2014> [cited 2014 23/07/2014]. Available from: <http://www.strokecenter.org/professionals/stroke-diagnosis/stroke-assessment-scales/>.
155. Lima-Silva TB, Bahia VS, Carvalho VA, Guimaraes HC, Caramelli P, Balthazar ML, et al. Direct and Indirect Assessments of Activities of Daily Living in Behavioral Variant Frontotemporal Dementia and Alzheimer Disease. *Journal of geriatric psychiatry and neurology*. 2014.

156. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke*. 2004;35(2):607-12.
157. Voepel-Lewis T, Malviya S, Tait AR. Validity of parent ratings as proxy measures of pain in children with cognitive impairment. *Pain management nursing : official journal of the American Society of Pain Management Nurses*. 2005;6(4):168-74.
158. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res*. 1975;12(3):189-98.
159. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. *CMAJ*. 2002;167(8):859-64.
160. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res*. 2009;43(4):411-31.
161. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*. 2005;53(4):695-9.
162. Luis CA, Keegan AP, Mullan M. Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *Int J Geriatr Psychiatry*. 2009;24(2):197-201.
163. Blackburn DJ, Bafadhel L, Randall M, Harkness KA. Cognitive screening in the acute stroke setting. *Age and ageing*. 2013;42(1):113-6.
164. Cumming TB, Churilov L, Linden T, Bernhardt J. Montreal Cognitive Assessment and Mini-Mental State Examination are both valid cognitive tools in stroke. *Acta neurologica Scandinavica*. 2013;128(2):122-9.
165. Godefroy O, Fickl A, Roussel M, Auribault C, Bugnicourt JM, Lamy C, et al. Is the Montreal Cognitive Assessment Superior to the Mini-Mental State Examination to Detect Poststroke Cognitive Impairment? A Study With Neuropsychological Evaluation. *Stroke*. 2011;42(6):1712-6.
166. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery After TIA and Stroke. *Stroke*. 2012;43(2):464-9.
167. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*. 2000;55(11):1613-20.
168. Gaber TA, Parsons F, Gautam V. Validation of the language component of the Addenbrooke's Cognitive Examination--Revised (ACE-R) as a screening tool for aphasia in stroke patients. *Australasian Journal of Ageing*. 2011;30(3):156-8.
169. Morris K, Hacker V, Lincoln NB. The validity of the Addenbrooke's Cognitive Examination-Revised (ACE-R) in acute stroke. *Disabil Rehabil*. 2012;34(3):189-95.
170. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry*. 2006;21(11):1078-85.

171. Torralva T, Roca M, Gleichgerrcht E, Bonifacio A, Raimondi C, Manes F. Validation of the Spanish Version of the Addenbrooke's Cognitive Examination-Revised (ACE-R). *Neurologia*. 2011;26(6):351-6.
172. Velayudhan L, Ryu SH, Raczek M, Philpot M, Lindsay J, Critchfield M, et al. Review of brief cognitive tests for patients with suspected dementia. *Int Psychogeriatr*. 2014;26(8):1247-62.
173. Hodkinson H. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age and ageing*. 1972;1:6.
174. Schofield I, Monaghan J, McFadyen A, Scott D, Tolson D, Nelson D. The validity of the 4-item Abbreviated Mental Test for older people in Accident and Emergency. *European Journal of Emergency Medicine*. 2010.
175. Schofield I, Stott DJ, Tolson D, McFadyen A, Monaghan J, Nelson D. Screening for cognitive impairment in older people attending accident and emergency using the 4-item Abbreviated Mental Test. *European journal of emergency medicine : official journal of the European Society for Emergency Medicine*. 2010;17(6):340-2.
176. Bonaiuto S, Rocca WA, Lippi A, Luciani P, Giannandrea E, Cavarzeran F, et al. Study on the validity of the Hodkinson Abbreviated Mental Test Score (AMTS) in detecting dementia of elderly subjects in appignano (Macerata province), Italy. *Arch Gerontol Geriatr*. 1992;15 Suppl 1:75-85.
177. Antonelli Incalzi R, Cesari M, Pedone C, Carosella L, Carbonin P. Construct validity of the abbreviated mental test in older medical inpatients. *Dementia and geriatric cognitive disorders*. 2003;15(4):8.
178. Chu L, Pei C, Ho M, Chan P. Validation of the Abbreviated mental Test (Hong Kong version) in the elderly medical patient. *Hong Kong Medical Journal* 1995;1(3):5.
179. Jitapunkul S, Pillay I, Ebrahim S. The abbreviated mental test: its use and validity. *Age and ageing*. 1991;20(5):332-6.
180. Harwood DM, Hope T, Jacoby R. Cognitive impairment in medical inpatients. II: Do physicians miss cognitive impairment? *Age and ageing*. 1997;26(1):37-9.
181. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. *Journal of the American Geriatrics Society*. 2008;56(5):823-30.
182. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-8.
183. Linn S. A new conceptual approach to teaching the interpretation of clinical tests. *Journal of Statistics Education*. 2004;12(3).
184. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (Iqcode) - Socio-Demographic Correlates, Reliability, Validity and Some Norms. *Psychological medicine*. 1989;19(4):1015-22.
185. McArthur K, Beagan ML, Degnan A, Howarth RC, Mitchell KA, McQuaige FB, et al. Properties of proxy-derived modified Rankin Scale assessment. *International journal of stroke : official journal of the International Stroke Society*. 2013;8(6):403-7.
186. Burton L, Tyson SF. Screening for cognitive impairment after stroke: a systematic review of psychometric properties and clinical utility. *Journal of rehabilitation medicine*. 2015;47(3):193-203.

187. Srikanth V, Thrift AG, Fryer JL, Saling MM, Dewey HM, Sturm JW, et al. The validity of brief screening cognitive instruments in the diagnosis of cognitive impairment and dementia after first-ever stroke. *Int Psychogeriatr*. 2006;18(2):295-305.
188. Schellinger PD, Bath PM, Lees KR, Bornstein NM, Uriel E, Eisert W, et al. Assessment of additional endpoints for trials in acute stroke - what, when, where, in who? *International Journal of Stroke*. 2012;7(3):227-30.
189. Yu KH, Cho SJ, Oh MS, Jung S, Lee JH, Shin JH, et al. Cognitive impairment evaluated with Vascular Cognitive Impairment Harmonization Standards in a multicenter prospective stroke cohort in Korea. *Stroke*. 2013;44(3):786-8.
190. Morales JM, Gonzalez-Montalvo JI, Bermejo F, Del-Ser T. The screening of mild dementia with a shortened Spanish version of the "Informant Questionnaire on Cognitive Decline in the Elderly". *Alzheimer disease and associated disorders*. 1995;9(2):105-11.
191. Radloff L. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977;1:385-401.
192. Roberts RE, Vernon SW. The Center for Epidemiologic Studies Depression Scale: its use in a community sample. *The American journal of psychiatry*. 1983;140(1):41-6.
193. Agrell B, Dehlin O. Comparison of six depression rating scales in geriatric stroke patients. *Stroke*. 1989;20(9):1190-4.
194. Parikh R, Mathai A, Parikh S, Sekhar GC, Thomas R. Understanding and using sensitivity, specificity and predictive values - Reply. *Indian J Ophthalmol*. 2008;56(4):341-.
195. Buist A, Condon J, Brooks J, Speelman C, Milgrom J, Hayes B, et al. Acceptability of routine screening for perinatal depression. *J Affect Disord*. 2006;93(1-3):233-7.
196. Johnston O, Fornai G, Cabrini S, Kendrick T. Feasibility and acceptability of screening for eating disorders in primary care. *Family practice*. 2007;24(5):511-7.
197. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361-70.
198. Bjellanda I, Dahlb A, Haugc T, Neckelmannd D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of Psychosomatic research*. 2002;52:9.
199. Aben I, Verhey F, Lousberg R, Lodder J, Honig A. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;43(5):386-93.
200. Mitchell AJ, Kaar S, Coggan C, Herdman J. Acceptability of common screening methods used to detect distress and related mood disorders-preferences of cancer specialists and non-specialists. *Psycho-oncology*. 2008;17(3):226-36.
201. Johnson G, Burvill PW, Anderson CS, Jamrozik K, Stewart-Wynne EG, Chakera TM. Screening instruments for depression and anxiety following stroke: experience in the Perth community stroke study. *Acta Psychiatr Scand*. 1995;91(4):252-7.
202. Scotland NNS. 2012 National Report : Stroke Services in Scottish Hospitals. In: (ISD) ISD, editor. 2012.
203. O'Rourke S, MacHale S, Signorini D, Dennis M. Detecting psychiatric morbidity after stroke: comparison of the GHQ and the HAD Scale. *Stroke*. 1998;29(5):980-5.

204. Sagen U, Vik TG, Moum T, Morland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the Montgomery and Asberg depression rating scale. *J Psychosom Res.* 2009;67(4):325-32.
205. Tang WK, Chan SSM, Chin HFK, Wong KS, Kwok TCY, Mok V, et al. Can the geriatric depression scale detect poststroke depression in Chinese elderly? *J Affect Disorders.* 2004;81(2):153-6.
206. Ferraro FR, Chelminski I. Preliminary normative data on the Geriatric Depression Scale-Short Form (GDS-SF) in a young adult sample. *Journal of clinical psychology.* 1996;52(4):443-7.
207. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. *Clinical Gerontologist.* 1982;1(1):6.
208. Watkins CL, Lightbody CE, Sutton CJ, Holcroft L, Jack CI, Dickinson HA, et al. Evaluation of a single-item screening tool for depression after stroke: a cohort study. *Clinical rehabilitation.* 2007;21(9):846-52.
209. Temple RO, Stern RA, Latham J, Ruffolo JS, Arruda JE, Tremont G. Assessment of mood state in dementia by use of the visual analog mood scales (VAMS). *Am J Geriatr Psychiatry.* 2004;12(5):527-30.
210. Mulley AG, Jr. Assessing patients' utilities. Can the ends justify the means? *Med Care.* 1989;27(3 Suppl):S269-81.
211. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Chapter 10: Analysing and Presenting Results 2010. In: *Cochrane Handbook for systematic Reviews of Diagnostic Test Accuracy* [Internet]. The Cochrane Collaboration; [61].
212. Zhu W, Zeng N, Wang N. Sensitivity, specificity, accuracy, associated confidence interval and ROC analysis with practical SAS implementations. *NESUG Proceedings.* 2010;Health Care and Life Sciences(November 14-17):9.
213. Berthier ML. Poststroke aphasia : epidemiology, pathophysiology and treatment. *Drugs Aging.* 2005;22(2):163-82.
214. Laska AC, Martensson B, Kahan T, von Arbin M, Murray V. Recognition of depression in aphasic stroke patients. *Cerebrovasc Dis.* 2007;24(1):74-9.
215. Laska AC. Aphasia in acute stroke. *Stockholm*2007.
216. Berg A, Palomaki H, Lehtihalmes M, Lonnqvist J, Kaste M. Poststroke depression: an 18-month follow-up. *Stroke.* 2003;34(1):138-43.
217. Schmid AA, Kroenke K, Hendrie HC, Bakas T, Sutherland JM, Williams LS. Poststroke depression and treatment effects on functional outcomes. *Neurology.* 2011;76(11):1000-5.
218. Dennis M, O'Rourke S, Lewis S, Sharpe M, Warlow C. Emotional outcomes after stroke: factors associated with poor outcome. *J Neurol Neurosurg Psychiatry.* 2000;68(1):47-52.
219. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC medical research methodology.* 2003;3:25.
220. de Rooij SE, Schuurmans MJ, van der Mast RC, Levi M. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *International Journal Geriatric Psychiatry.* 2005;20(7):609-15.

221. McDowd JM, Filion DL, Pohl PS, Richards LG, Stiers W. Attentional abilities and functional outcomes following stroke. *Journal of Gerontology Series B, Psychological Sciences and Social Sciences*. 2003;58(1):P45-53.
222. Kirkwood BR, J.A.C S. *Essential Medical Statistics*. USA: Massachusetts: Blackwell Science; 2003.
223. Malik A, Turner M, Sohail M, Potter P, Sadler C, Salcido R, et al. *Neuropsychological Evaluation* 2013 15/04/2014. Available from: <http://emedicine.medscape.com/article/317596-overview>.
224. Holmes J, Gilbody S. Differences in use of abbreviated mental test score by geriatricians and psychiatrists. *Brit Med J*. 1996;313(7055):465-.
225. McKeith IG, Fairbairn AF, Bothwell RA, Moore PB, Ferrier IN, Thompson P, et al. An evaluation of the predictive validity and inter-rater reliability of clinical diagnostic criteria for senile dementia of Lewy body type. *Neurology*. 1994;44(5):872-7.
226. Ghiselli EE. The Prediction of Predictability. *Educ Psychol Meas*. 1960;20(1):3-8.
227. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Bmj*. 2008;337:a1655.
228. Royal College of Physicians. *National Clinical Guidelines for Stroke In: Clinical Effectiveness and evaluation Unit RCoP, editor*. 3 ed. London Royal College of Physicians 2008.
229. Hart S, Morris R. Screening for depression after stroke: an exploration of professionals' compliance with guidelines. *Clinical rehabilitation*. 2008;22(1):60-70.
230. Toniolo S. Neuropsychological interventions in stroke survivors: implications for evidence based psychological practice. *Giornale italiano di medicina del lavoro ed ergonomia*. 2011;33(1 Suppl A):A29-36.
231. Bunn F, Goodman C, Sworn K, Rait G, Brayne C, Robinson L, et al. Psychosocial factors that shape patient and carer experiences of dementia diagnosis and treatment: a systematic review of qualitative studies. *PLoS medicine*. 2012;9(10):e1001331.
232. Draper B, Peisah C, Snowdon J, Brodaty H. Early dementia diagnosis and the risk of suicide and euthanasia. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2010;6(1):75-82.
233. Broderick JE, Vikingstad G. Frequent assessment of negative symptoms does not induce depressed mood. *Journal of clinical psychology in medical settings*. 2008;15(4):296-300.
234. Fox C, Lafortune L, Boustani M, Brayne C. The pros and cons of early diagnosis in dementia. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2013;63(612):e510-2.
235. Turner S, Iliffe S, Downs M, Wilcock J, Bryans M, Levin E, et al. General practitioners' knowledge, confidence and attitudes in the diagnosis and management of dementia. *Age and ageing*. 2004;33(5):461-7.
236. Hobson JP, Leeds L, Meara RJ. The feasibility of cognitive screening of patients with ischaemic stroke using the preliminary neuropsychological battery. *Psychol Health*. 2003;18(5):655-65.
237. Duncan PW, Zorowitz R, Bates B, Choi JY, Glasberg JJ, Graham GD, et al. Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. *Stroke*. 2005;36(9):e100-43.

238. Kneebone, II, Neffgen LM, Pettyfer SL. Screening for depression and anxiety after stroke: developing protocols for use in the community. *Disabil Rehabil.* 2012;34(13):1114-20.
239. Blake H, McKinney M, Treece K, Lee E, Lincoln NB. An evaluation of screening measures for cognitive impairment after stroke. *Age and ageing.* 2002;31(6):451-6.
240. Burns KE, Duffett M, Kho ME, Meade MO, Adhikari NK, Sinuff T, et al. A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ.* 2008;179(3):245-52.
241. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J Med Internet Res.* 2004;6(3):e34.
242. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care.* 2003;15(3):261-6.
243. NHS National Services Scotland. Scottish Stroke Care Audit Stroke Care Audit Homepage: ISD Scotland; 2012 [April]. Available from: <http://www.strokeaudit.scot.nhs.uk>.
244. Patel M, Coshall C, Rudd AG, Wolfe CD. Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clinical rehabilitation.* 2003;17(2):158-66.
245. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2011;42(9):2672-713.
246. Agrell B, Dehlin O. Mini mental state examination in geriatric stroke patients. Validity, differences between subgroups of patients, and relationships to somatic and mental variables. *Aging (Milano).* 2000;12(6):439-44.
247. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, Kappelle LJ, de Haan EH. Restrictions of the Mini-Mental State Examination in acute stroke. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists.* 2005;20(5):623-9.
248. Townend B, Whyte S, Desborough T, Crimmins D, Markus R, Levi C, et al. Longitudinal prevalence and determinants of early mood disorder post-stroke. *Journal of Clinical Neuroscience* 2006;14:6.
249. Tang WK, Ungvari GS, Chiu HF, Sze KH, Yu AC, Leung TL. Screening post-stroke depression in Chinese older adults using the hospital anxiety and depression scale. *Aging Ment Health.* 2004;8(5):397-9.
250. Thomas SA, Walker MF, Macniven JA, Haworth H, Lincoln NB. Communication and Low Mood (CALM): a randomized controlled trial of behavioural therapy for stroke patients with aphasia. *Clinical rehabilitation.* 2013.
251. Saver JL, Kidwell CS, Liebeskind DS, Starkman S. Acute ischemic stroke trials. *Stroke.* 2001;32(1):275-8.
252. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. *JAMA.* 2011;306(24):2670-2.
253. Lees R, Fearon P, Harrison JK, Broomfield NM, Quinn TJ. Cognitive and mood assessment in stroke research: focused review of contemporary studies. *Stroke.* 2012;43(6):1678-80.
254. Chodosh J, Petitti DB, Elliott M, Hays RD, Crooks VC, Reuben DB, et al. Physician recognition of cognitive impairment: evaluating the need for improvement. *Journal of the American Geriatrics Society.* 2004;52(7):1051-9.

255. Royal College of Physicians R. National Clinical Guidelines for Stroke - Forth Edition In: The Clinical Effectiveness and Evaluation Unit C, editor. Forth Edition ed. London: The Royal College of Physicians; 2012. p. 232.
256. Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. ed: The Cochrane Collaboration; 2009.
257. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-94.
258. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-12.
259. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. Impact of different operational definitions on mild cognitive impairment rate and MMSE and MoCA performance in transient ischaemic attack and stroke. *Cerebrovasc Dis*. 2013;36(5-6):355-62.
260. Davis DHJ, Creavin ST, Noel-Storr A, Quinn TJ, Smailagic N, Hyde C, et al. Cochrane Db Syst Rev [Internet]. Group CDaCI, editor. The Cochrane Library: The Cochrane Collaboration. 2013. [cited 2013].
261. F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Protocol) [Internet]. The Cochrane Collaboration. 2013.
262. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-36.
263. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nature Reviews Neurology*. 2009;5(4):210-20.
264. Takwoingi Y, Deeks JJ. MetaDAS: A SAS macro for meta-analysis of diagnostic accuracy studies. Quick reference and worked example. User Guide Version 13 [Internet]. 2010 July Available from: <http://srdta.cochrane.org/>.
265. Mitchell AJ. Sensitivity x PPV is a recognized test called the clinical utility index (CUI+). *Eur J Epidemiol*. 2011;26(3):251-2.
266. Baum CM, Connor LT, Morrison T, Hahn M, Dromerick AW, Edwards DF. Reliability, validity, and clinical utility of the Executive Function Performance Test: a measure of executive function in a sample of people with stroke. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*. 2008;62(4):446-55.
267. Cumming TB, Blomstrand C, Bernhardt J, Linden T. The NIH stroke scale can establish cognitive function after stroke. *Cerebrovasc Dis*. 2010;30(1):7-14.
268. Green S, Sinclair E, Rodgers E, Birks E, Lincoln N. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for post stroke cognitive impairment screening. *International Journal of Therapy and Rehabilitation*. 2013;20(11):7.
269. Salvadori E, Pasi M, Poggesi A, Chiti G, Inzitari D, Pantoni L. Predictive value of MoCA in the acute phase of stroke on the diagnosis of mid-term cognitive impairment. *J Neurol*. 2013;260(9):2220-7.

270. Wolf TJ, Stift S, Connor LT, Baum C, Cognitive Rehabilitation Research G. Feasibility of using the EFPT to detect executive function deficits at the acute stage of stroke. *Work*. 2010;36(4):405-12.
271. Bour A, Rasquin S, Boreas A, Limburg M, Verhey F. How predictive is the MMSE for cognitive performance after stroke? *Journal of Neurology*. 2010;257(4):630-7.
272. Desmond DW, Tatemichi TK, Hanzawa L. The Telephone Interview for Cognitive Status (Tics) - Reliability and Validity in a Stroke Sample. *Int J Geriatr Psych*. 1994;9(10):803-7.
273. Larson E, Kirschner K, Bode R, Heinemann A, Goodman R. Construct and predictive validity of the repeatable battery for the assessment of neuropsychological status in the evaluation of stroke patients. *J Clin Exp Neuropsychol*. 2005;27(1):16-32.
274. Pendlebury ST, Welch SJ, Cuthbertson FC, Mariz J, Mehta Z, Rothwell PM. Telephone Assessment of Cognition After Transient Ischemic Attack and Stroke: Modified Telephone Interview of Cognitive Status and Telephone Montreal Cognitive Assessment Versus Face-to-Face Montreal Cognitive Assessment and Neuropsychological Battery. *Stroke*. 2013;44(1):227-9.
275. Brookes RL, Hannesdottir K, Lawrence R, Morris RG, Markus HS. Brief Memory and Executive Test: evaluation of a new screening test for cognitive impairment due to small vessel disease. *Age and ageing*. 2012;41(2):212-8.
276. Cartoni A, Lincoln NB. The sensitivity and specificity of the Middlesex Elderly Assessment of Mental State (MEAMS) for detecting cognitive impairment after stroke. *Neuropsychol Rehabil*. 2005;15(1):55-67.
277. de Koning I, Dippel DW, van Kooten F, Koudstaal PJ. A short screening instrument for poststroke dementia : the R-CAMCOG. *Stroke*. 2000;31(7):1502-8.
278. de Koning I, van Kooten F, Koudstaal PJ, Dippel DW. Diagnostic value of the Rotterdam-CAMCOG in post-stroke dementia. *J Neurol Neurosurg Psychiatry*. 2005;76(2):263-5.
279. Dong Y, Venketasubramanian N, Chan BP, Sharma VK, Slavin MJ, Collinson SL, et al. Brief screening tests during acute admission in patients with mild stroke are predictive of vascular cognitive impairment 3-6 months after stroke. *J Neurol Neurosurg Psychiatry*. 2012;83(6):580-5.
280. Dong YH, Sharma VK, Chan BPL, Venketasubramanian N, Teoh HL, Seet RCS, et al. The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *Journal of the neurological sciences*. 2010;299(1-2):15-8.
281. Grace J, Nadler JD, White DA, Guilmette TJ, Giuliano AJ, Monsch AU, et al. Folstein vs modified Mini-Mental State Examination in geriatric stroke. Stability, validity, and screening utility. *Archives of neurology*. 1995;52(5):477-84.
282. Hershey LA, Jaffe DF, Greenough PG, Yang SL. Validation of cognitive and functional assessment instruments in vascular dementia. *International journal of psychiatry in medicine*. 1987;17(2):183-92.
283. Jodzio K, Biechowska D. Wisconsin card sorting test as a measure of executive function impairments in stroke patients. *Applied neuropsychology*. 2010;17(4):267-77.
284. Tang WK, Mok V, Chan SS, Chiu HF, Wong KS, Kwok TC, et al. Screening of dementia in stroke patients with lacunar infarcts: comparison of the mattis dementia rating scale and the mini-mental state examination. *Journal of geriatric psychiatry and neurology*. 2005;18(1):3-7.

285. Wong A, Xiong YY, Kwan PW, Chan AY, Lam WW, Wang K, et al. The validity, reliability and clinical utility of the Hong Kong Montreal Cognitive Assessment (HK-MoCA) in patients with cerebral small vessel disease. *Dementia and geriatric cognitive disorders*. 2009;28(1):81-7.
286. Wu Y, Wang M, Ren M, Xu W. The effects of educational background on Montreal Cognitive Assessment screening for vascular cognitive impairment, no dementia, caused by ischemic stroke. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2013;20(10):1406-10.
287. Nokleby K, Boland E, Bergersen H, Schanke AK, Farner L, Wagle J, et al. Screening for cognitive deficits after stroke: a comparison of three screening tools. *Clinical rehabilitation*. 2008;22(12):1095-104.
288. de Koning I, van Kooten F, Dippel DW, van Harskamp F, Grobbee DE, Kluft C, et al. The CAMCOG: a useful screening instrument for dementia in stroke patients. *Stroke*. 1998;29(10):2080-6.
289. Johnson-Greene D, Touradji P, Emmerson LC. The Three Cities Test: Preliminary Validation of a Short Bedside Memory Test in Persons with Acute Stroke. *Topics in Stroke Rehabilitation*. 2009;16(5):321-9.
290. Lees R, Corbet S, Johnston C, Moffitt E, Shaw G, Quinn TJ. Test accuracy of short screening tests for diagnosis of delirium or cognitive impairment in an acute stroke unit setting. *Stroke*. 2013;44(11):3078-83.
291. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. *Stroke*. 2010;41(6):1290-3.
292. Wong A, Mok VC, Yim P, Fu M, Lam WW, Yau C, et al. The executive clock drawing task (CLOX) is a poor screening test for executive dysfunction in Chinese elderly patients with subcortical ischemic vascular disease. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2004;11(5):493-7.
293. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Brit Med J*. 2003;326(7379):41-4.
294. Kutlubaev MA. [Detection of cognitive deficit in a therapist's practice: review of screening scales]. *Ter Arkh*. 2014;86(11):135-8.
295. Schuetz GM, Schlattmann P, Dewey M. Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies. *Brit Med J*. 2012;345.
296. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry*. 2007;78(8):790-9.
297. Barber M, Stott DJ. Validity of the Telephone Interview for Cognitive Status (TICS) in post-stroke subjects. *Int J Geriatr Psychiatry*. 2004;19(1):75-9.
298. Mayo NE, Korner-Bitensky NA, Becker R. Recovery time of independent function post-stroke. *American Journal of Physical Medicine and Rehabilitation* 1991;70(1):5-12.
299. Farrell TW, Dosa D. The assessment and management of hypoactive delirium. *Medicine and health, Rhode Island*. 2007;90(12):393-5.

300. Association TS. Feeling overwhelmed: The emotional impact of stroke. <http://www.stroke.org.uk>: 2013.
301. Singh A, Black SE, Herrmann N, Leibovitch FS, Ebert PL, Lawrence J, et al. Functional and neuroanatomic correlations in poststroke depression: the Sunnybrook Stroke Study. *Stroke*. 2000;31(3):637-44.
302. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biol Psychiatry*. 2002;52(3):253-64.
303. King RB, Shade-Zeldow Y, Carlson CE, Feldman JL, Philip M. Adaptation to stroke: a longitudinal study of depressive symptoms, physical health, and coping process. *Top Stroke Rehabil*. 2002;9(1):46-66.
304. Sibolt G, Curtze S, Melkas S, Pohjasvaara T, Kaste M, Karhunen PJ, et al. Post-stroke depression and depression-executive dysfunction syndrome are associated with recurrence of ischaemic stroke. *Cerebrovasc Dis*. 2013;36(5-6):336-43.
305. Lincoln NB, Jackson JM, Edmans JA, Walker MF, Farrow VM, Latham A, et al. The accuracy of predictions about progress of patients on a stroke unit. *J Neurol Neurosurg Psychiatry*. 1990;53(11):972-5.
306. Caeiro L, Ferro JM, Santos CO, Figueira ML. Depression in acute stroke. *J Psychiatry Neurosci*. 2006;31(6):377-83.
307. Sibon I, Lassalle-Lagadec S, Renou P, Swendsen J. Evolution of depression symptoms following stroke: a prospective study using computerized ambulatory monitoring. *Cerebrovasc Dis*. 2012;33(3):280-5.
308. Turner-Stokes L, Kalmus M, Hirani D, Clegg F. The Depression Intensity Scale Circles (DISCs): a first evaluation of a simple assessment tool for depression in the context of brain injury. *J Neurol Neurosurg Psychiatry*. 2005;76(9):1273-8.
309. Dawkins N, Cloherty ME, Gracey F, Evans JJ. The factor structure of the Hospital Anxiety and Depression Scale in acquired brain injury. *Brain Inj*. 2006;20(12):1235-9.
310. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33;quiz 4-57.
311. World Health Organisation (WHO). The ICD-10 classification of mental and behavioural disorders. Diagnostic criteria for research. Geneva 1993.
312. Duburcq A, Blin P, Charpak Y, Blachier C, Allicar MP, Bouhassira M, et al. Use of a structured diagnostic interview to identify depressive episodes in an epidemiologic study: a posteriori internal validation. *Rev Epidemiol Sante*. 1999;47(5):455-63.
313. Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data*. Second Edition ed. Oxford, UK: Oxford University Press; 2002.
314. Information Services Division of National Services Scotland. Scottish Stroke care audit: about the audit <http://www.strokeaudit.scot.nhs.uk/2014> [updated 06/02/2015; cited 2015 26/02/2015].
315. Broomfield N, Scoular A, Welsh P, Walters M, Evans J. Poststroke anxiety is prevalent at the population level, especially among socially deprived and younger age community stroke survivors. *International Journal of Stroke*. 2015;10(6):6.
316. Kneebone I, Walker-Samuel N, Swanston J, Otto E. Relaxation training after stroke: potential to reduce anxiety. *Disabil Rehabil*. 2013.

317. Williams LS, Brizendine EJ, Plue L, Bakas T, Tu W, Hendrie H, et al. Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke*. 2005;36(3):635-8.
318. Quaranta D, Marra C, Gainotti G. Mood disorders after stroke: diagnostic validation of the poststroke depression rating scale. *Cerebrovasc Dis*. 2008;26(3):237-43.
319. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864-70.
320. Ankolekar S, Renton C, Sprigg N, Bath PM. The cog-4 subset of the national institutes of health stroke scale as a measure of cognition: relationship with baseline factors and functional outcome after stroke using data from the virtual international stroke trials archive. *Stroke Res Treat*. 2013;2013:562506.
321. Hajjar K, Fulton RL, Diener HC, Lees KR, the VC. Does the cognitive measure Cog-4 show improvement among patients treated with thrombolysis after acute stroke? *International Journal of Stroke*. 2012.
322. Gottesman RF, Kleinman JT, Davis C, Heidler-Gary J, Newhart M, Hillis AE. The NIHSS-plus: improving cognitive assessment with the NIHSS. *Behavioural neurology*. 2010;22(1-2):11-5.
323. Noel-Storr AH, McCleery JM, Richard E, Ritchie CW, Flicker L, Cullum SJ, et al. Reporting standards for studies of diagnostic test accuracy in dementia: The STARDdem Initiative. *Neurology*. 2014.
324. Curran CA, Ponsford JL, Crowe S. Coping strategies and emotional outcome following traumatic brain injury: a comparison with orthopedic patients. *Journal of Head Trauma Rehabilitation*. 2000;15(6):1256-74.
325. Elliott R. Executive functions and their disorders. *Brit Med Bull*. 2003;65:49-59.
326. Damian AM, Jacobson SA, Hentz JG, Belden CM, Shill HA, Sabbagh MN, et al. The Montreal Cognitive Assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores. *Dementia and geriatric cognitive disorders*. 2011;31(2):126-31.
327. Ankolekar S, Renton C, Sprigg N, Bath P. The Cog-4 subset of the national Institutes of health Stroke Scale as a Measure of Cognition: relationship with Baseline Factors and Functional Outcome after Stroke Using Data from the Virtual International Stroke Trials Archive. *Stroke Research and Treatment*. 2013;2013:6.
328. Riepe MW, Riss S, Bittner D, Huber R. Screening for cognitive impairment in patients with acute stroke. *Dementia and geriatric cognitive disorders*. 2004;17(1-2):49-53.
329. Schmidt R, Mechtler L, Kinkel PR, Fazekas F, Kinkel WR, Freidl W. Cognitive impairment after acute supratentorial stroke: a 6-month follow-up clinical and computed tomographic study. *European archives of psychiatry and clinical neuroscience*. 1993;243(1):11-5.
330. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society*. 1992;40(9):922-35.
331. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology*. 2009;73(21):1738-45.
332. Crawford S, Whitnall L, Robertson J, Evans JJ. A systematic review of the accuracy and clinical utility of the Addenbrooke's Cognitive Examination and the Addenbrooke's Cognitive

- Examination-Revised in the diagnosis of dementia. *Int J Geriatr Psychiatry*. 2012;27(7):659-69.
333. Lerner AJ. Addenbrooke's Cognitive Examination-Revised (ACE-R) in day-to-day clinical practice. *Age and ageing*. 2007;36(6):685-6.
334. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire*. *JAMA*. 1999;282(18):1737-44.
335. Mahoney J, Drinka TJ, Abler R, Gunter-Hunt G, Matthews C, Gravenstein S, et al. Screening for depression: single question versus GDS. *Journal of the American Geriatrics Society*. 1994;42(9):1006-8.
336. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiat*. 1989;46(11):1006-11.
337. Watkins C, Daniels L, Jack C, Dickinson H, van Den Broek M. Accuracy of a single question in screening for depression in a cohort of patients after stroke: comparative study. *Bmj*. 2001;323(7322):1159.
338. Department of Health. Using the Commissioning for Quality and Innovation (CQUIN) payment framework: Guidance on new national goals for 2012-13 In: *Dementia SCP-OP*, editor. Leeds (UK)2012. p. 1-33.